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STEPS TOWARD A BETTER UNDERSTANDING OF THE ACUTE ALLERGIC REACTION

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THE BETTER we understand the physiology and immunology of the acute allergic reaction, the better we shall be able to treat our patients suffering from clinical manifestations of this reaction. Information regarding the various steps in the acute reaction is increasing. This information has been diagrammed following the lead of Trethewie,[105] Raffel,[83] and Mongar and Schild;[73] incorporating the concepts of Boyd[8] and revising a previous diagram.[61] As MacKay[64] explained, such a diagram or model will " 'subtract out' what we think we understand, so that what is not yet understood is revealed more clearly."

Immunologic mechanisms in the lower animals and in human beings were presumably devised for their protection against harmful contacts in their environment. The interesting observation of Dienes[23] that both atopic patients and those suffering from worm infestations produce similar reagin-type antibodies needs further study. In addition, it is of interest that eospinophilia is common to both types of patients.

It is well known that allergy in human beings and anaphylaxis in lower animals differ somewhat. However, experimental study of anaphylaxis has been of great help in understanding the acute allergic reaction in human beings.

Figure 1 presents a scheme of the mechanism of the acute allergic reaction as it is presently conceived.

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ENTRANCE OF ANTIGEN INTO BODY

The first step in the mechanism of acute allergic reaction is the entrance of some antigen into the body. The antigen must be complete or it must be a haptene that is either combined with protein or able to combine

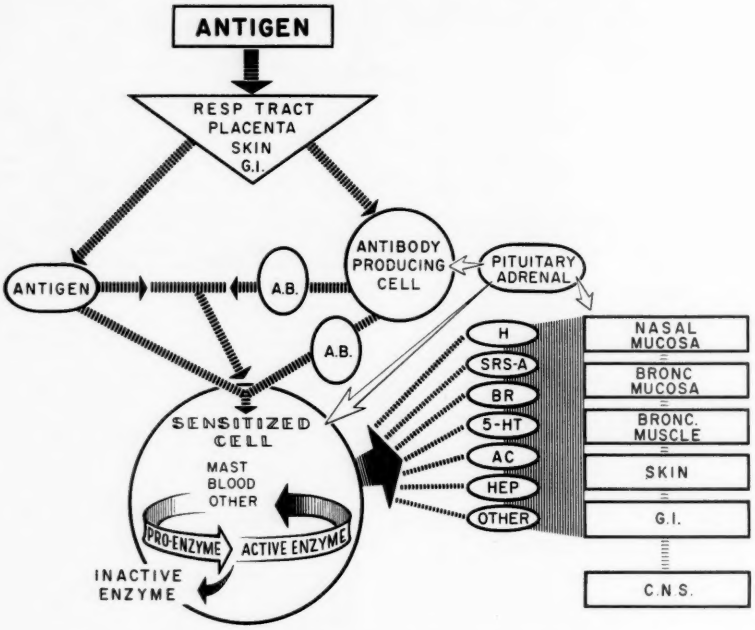

Fig. 1. Diagram of mechanism of the acute allergic reaction.

with tissue proteins to form a complete antigen.[8] The common sites of entrance into the body are the respiratory tract, skin and gastrointestinal tract. It is also probable that certain antigens may cross the placental barrier to the fetus from the mother.[84]

PRODUCTION OF ANTIBODIES

The site of the initial entrance of the antigen to the body may make little difference in the immediate type of reaction. Initially some of the antigen reaches an antibody-producing cell either directly or after being acted on by a macrophage. A specific cell type is not named in the diagram (Fig. 1). Certain lymphoid cells, however, are recognized as the antibody-producing cells. Those known to produce antibodies are as follows: (1) the plasma cell without Russell bodies (Marschalko type), (2) the plasma cells with Russell bodies and (3) the lymphoid cell in the germinal centers of lymphatic nodules.[77] Some workers[32,52,59] have

implicated only the plasma cell, whereas others[28,29,116] have implicated only the lymphoid cell.

As recently as 1953, McMaster[67] cautioned investigators about accepting the evidence up to that time as favoring either the plasma cell or the lymphocyte. Good,[44] in 1956, however, believed that there was sufficient evidence to support the importance of the plasma cell in antibody formation. At present, the suggestion of Ortega and Mellors[77] seems reasonable: that each of the three morphologically distinct categories of cells that synthesize gamma globulin (antibody) represents a response to a particular form of antigenic stimulation. However, the evidence of Dixon and co-workers[25] and of Fitch and co-workers[37] may indicate that the lymphocyte is concerned with the "adaptation phase" and the plasma cells with the "production phase" of antibody production, or that the plasma cell is the morphologic expression of antibody production.[43] It is also possible, as Ortega and Mellors[77] suggested, that each of the three morphologically distinct categories of cells that synthesize gamma globulin (antibody) may represent a response to a particular form of antigenic stimulation.

In human allergic disease, investigators are concerned with an antibody that differs in some respects from most if not all others. There is even some question whether reagin (skin-sensitizing antibody, reaginic antibody) is a real antibody. Efforts to settle this point by protein electrophoresis have yielded conflicting evidence. The terms "gamma globulin" and "antibody" probably can be used synonymously, since all of the usual antibodies have been shown to be gamma globulin and it is probable that all gamma globulin is antibody.

Studies of serum from allergic persons have been carried out with the Tiselius apparatus, the starch-block apparatus, and the electrophoresis-convection apparatus. Results indicate that skin-sensitizing antibody may be in the alpha-2, the beta, or the gamma globulin fractions.[12,13,96-98] The line drawn between beta globulin and gamma globulin is often arbitrary, and therefore these fractions may overlap.[13] Present evidence suggests that reagin is most likely beta globulin. On the other hand, certain host differences may allow the usual antibody-producing cells to produce reagin.

The mechanism of antibody production in the cell is still uncertain. Three theories are currently extant: (1) the template theory of Haurowitz,[50] Alexander,[1] and Mudd[74] and modified by Pauling,[81] (2) the adaptive-enzyme or self-marker concept of Burnet[11] and (3) the natural-selection theory of Jerne.[54] Whether the skin-sensitizing antibody is produced by a variation of one of these mechanisms is still unknown. About ten days are needed for sensitization to develop after introduction of the antigen. The antibody (reagin) produced may be demonstrated in the blood stream and also in the skin. Antibodies in the blood stream may be demonstrated by the passive transfer test (Prausnitz-Küstner reaction), and those in the skin by the scratch or intradermal skin test. If blood from a sensitized person is transfused to a nonsensitized person,

reagin may be demonstrated in the recipient's blood for only a short time but it may be demonstrated in the skin cells for several weeks.[99]

Which cells in the skin become sensitized is not known. It is tempting to think that the mast cells, not only in the skin but also elsewhere in the body, are the cells affected. Other cells, of course, may be involved also. Dale[17] has considered the smooth-muscle cells of the bronchioles to be sensitized. Cells in the blood may be sensitized as well.[57,76,109]

ANTIGEN-ANTIBODY REACTION

When antigen is next introduced into the circulation it is met by antibody. There is some uncertainty whether union of the two takes place in the blood stream, or in or on the sensitized cell. Perhaps union occurs in both places; at least there is experimental evidence to support this view.

As long ago as 1909, Friedberger[38] and Friedemann[39] found independently that if antibody and antigen were combined a precipitate formed. (They were not working with reagin.) This precipitate, if incubated with normal serum, yielded a toxic principle. Bordet,[7] in 1913, found that a similar toxic principle could be produced by incubating agar or starch or some other polysaccharide with normal serum. This toxic principle was given the name "anaphylatoxin."

From 1913 to 1920, the work of Dale[20] and his group produced evidence of direct cellular reaction. He[18] and Schultz[94] independently showed that the contact of antigen with sensitized tissues caused reaction even in the the absence of blood or serum. According to Dale,[19] histamine or histamine-like substance is released by the reaction of antigen and sensitized cell. This was demonstrated by Manwaring,[65] by Gebauer-Fuelnegg and associates,[41] by Bartosch and associates,[2] and by Dale[20] himself. The anaphylatoxin concept was virtually abandoned during the period 1922 to 1940. Then Rocha e Silva[87,88] revived interest in anaphylatoxin and was able to demonstrate that it released histamine in the guinea pig.

Thus, two presumably different mechanisms were found to exert their action through a final common pathway: histamine release. It seems best at present to accept the probability of a dual mechanism rather than to insist on one or the other.

Next to be considered is the sensitized cell or cells. Such cells should contain the various chemical compounds that are released by the antigen-antibody reaction. The mast cell contains or makes many of these.[40] Its circulating analogue, the basophil, probably contains most of the histamine in the blood in human beings.[46,108] Evidence of the tissue cells that may be involved is lacking. One or more of the other circulating blood cells also may be involved.

Histamine and serotonin (5-hydroxytryptamine) have been found in platelets.[6,31] The work of Katz[57] demonstrated release of histamine from the sensitized blood cells (chiefly leukocytes but also erythrocytes) of dogs,

guinea pigs and rabbits *in vitro*. Noah and Brand[76] found histamine release *in vitro* from blood cells of ragweed-sensitized persons. VanArsdel and co-workers[109] have also demonstrated the *in vitro* release of histamine when human blood is incubated with the antigen to which the person is sensitive. Investigators are still uncertain about which blood cell concerned with *in vivo* release of histamine or other mediators in human beings is most important.

Knowledge of the mast cell and its importance is still poorly recognized by many clinicians. According to Michels,[69] it was first named by Ehrlich[30] in 1879 and was originally considered an overnourished connective tissue cell. Hence, the name from the German word meaning "feeding." Ehrlich first noted cells of this type at sites of chronic inflammation. They were considered of little practical importance until the study of their cytochemistry was begun about 1935.[117] Staemmler,[104] however, in 1921 had called attention to the possibility of their being unicellular "glands" of connective tissue for the production of mucin. In studies made between 1935 and 1946, Jorpes[55] found that mast cells contain heparin. During that period and into 1950 evidence was accumulating that these cells could also release hyaluronic acid. It was not until 1953, however, that Riley[86] demonstrated that mast cells probably contain histamine. Subsequent work by him and others has amply confirmed this finding.[40] Most recently, 5-hydroxytryptamine has been isolated from mast cells.[3] Evidence has been presented, however, that mast cells may not be as important releasers of 5-hydroxytryptamine as was originally thought.[40,78,114] Studies[114] show that the 5-hydroxytryptamine content of mast cells varies considerably with the species of animal: mast cells of the guinea pig, dog, man, cow, horse, rabbit, ox, hog, hamster and cat contain little or no 5-hydroxytryptamine, while those of the rat and mouse may contain a little. It is not known whether mast cells contain or can make Slow Reacting Substance-A or acetylcholine.

A mechanism by which histamine may be released from the cell has been formulated recently by Mongar and Schild.[72,73] In Figure 1, this is indicated by the ribboned lettering. Mongar and Schild present evidence for an enzyme precursor (pro-enzyme) in the cell which is inactivated quickly under normal circumstances when it becomes active. Under other circumstances (at the time antigen-antibody and pro-enzyme are united) the active enzyme remains active and releases histamine. It should be stated, however, that some earlier evidence has been against the acceptance of enzyme release.[66] The work of Mongar and Schild demonstrated that release of histamine by the antigen-antibody reaction differs from that by chemical releasers such as 48/80 and octylamine. The release of histamine by the antigen-antibody reaction takes place only in the intact cell and is retarded by anoxia. The drugs release histamine from either the intact cell or the cell particles, and anoxia accelerates the release.

Uvnäs[107] has recently reviewed this and other mechanisms by which

histamine is released. He proposed a theory of release which may combine the two divergent theories: (1) that the liberation of histamine is due to an enzymatic mechanism and (2) that histamine is stored in mast-cell granules in weak (ionic) linkages which do not require enzymatic processes for their dissolution. He envisions a mechanism (in which 48/80 is the liberator) by which the drug activates a lytic enzyme which is already present on the surface of the cell but which is kept inactive by an inhibitor. Removal of the inhibitor by 48/80 allows the lytic enzyme to become active. It is his opinion also that several enzyme mechanisms may be triggered, as has been suggested by Junqueira and Beiguelman.[56]

Uvnäs[107] described, only to refute, a displacement theory originally proposed by MacIntosh and Paton.[63] According to this theory, histamine is replaced in the mast-cell granules by the releasing substances. This displacement theory has recently received additional support from Smith.[100]

Further work is necessary to establish with certainty which mechanism is correct. Additional work also must be done to establish the mechanism of release of the other chemical mediators.

SUBSTANCES RELEASED BY ANTIGEN-ANTIBODY REACTION

Evidence now exists that histamine[72,93], heparin,[53] 5-hydroxytryptamine,[111] acetylcholine,[75,112] slow-reacting substances[9,110] and perhaps others may be released by the antigen-antibody reaction. Some of the actions of these compounds are listed in the table. Their action is primarily on blood vessels and smooth muscle. Further study may reveal that some of these substances produce their action by effecting the release of one of the other substances or by inhibiting the destroying enzyme of another.[31,111] Likewise, one may be more important in one species than in another. This concept of a release of several substances would be compatible with Dale's[17] concept of the origin of the threefold response, namely, that the response is attributable "probably not [to] histamine itself, but rather to an 'H-complex' . . . in the sense of a mixture of histamine itself with other natural . . . vasodilator substances, all readily released from the cell-protoplasm . . . and producing a combined reaction in which, however, the effects of the intensely active histamine would clearly predominate."

The galaxy of released substances (chemical mediators) listed in the table is an interesting group of compounds, and each substance merits a brief comment.

Histamine is widely distributed in the body. The quantity varies from one organ to another, and an organ such as the liver, which is rich in histamine in some species, such as the rabbit, may have little histamine in another species, such as the guinea pig.[35] The histamine content of tissue parallels that of the mast cell.[113] Most workers feel that histamine plays an important but not an exclusive role in the causation of allergic disease. The histamine-destroying enzyme has been called "histaminase,"

though some feel that it is more nearly correct to designate the enzyme "diamine oxidase."

Parrot and Laborde[80] have reported what is probably another mechanism of histamine inactivation which they term "histaminopexic." Histaminopexic activity of the blood serum is said to be present in normal persons but absent in those having allergic disease.

TABLE I. SOME ACTIONS OF SUBSTANCES CONSIDERED TO BE RELEASED BY ANTIGEN-ANTIBODY REACTION

Substance	Dilates Small Vessels	Constricts Bronchi	Decreases Coagulability of Blood
Histamine	+	+	0
Slow-reacting substance A (SRS-A)	0	+	0
Bradykinin	+	0	0
5-hydroxytryptamine (serotonin)	Constricts	+	0
Acetylcholine	+	+	0
Heparin	0	0	+

One of the early criticisms of the histamine-release theory was that this could not explain the increased coagulability of the blood in anaphylactic shock. In 1941, Jaques and Waters[35] found that *heparin* was released. The simultaneous release of histamine and heparin was demonstrated subsequently.[95] The former series of studies included one showing that the mast cells of the canine liver were reduced in number after anaphylactic shock. The presence of heparin in mast cells has already been mentioned. It also occurs in muscle. Heparinase has been described, though most of the heparin is excreted by the kidney either in depolymerized or active form.[45,55]

5-Hydroxytryptamine is present in the gastrointestinal tract, blood platelets, spleen, brain and lungs.[31,111] The content in the lung varies in different animal species. Some workers feel that 5-hydroxytyptamine is stored mainly in platelets.[14] Although it has been found in mast cells in rats,[3,14] West[114] has pointed out that high values for this substance and histamine do not occur in the same tissue. It seems possible for one substance to be released without release of the other. There is some evidence that 5-hydroxytrytamine can act as a histamine releaser.[31]

Reserpine releases 5-hydroxytryptamine, while lysergic acid diethylamide and Bol. 148 (2-bromo-lysergic acid diethylamide) antagonize it.[79] Lysergic acid diethylamide is not suitable for use in man though Bol. 148 has been administered. It should also be pointed out that 48/80 may release 5-hydroxytryptamine as well as histamine, though this may be noted only in the rat.[5] Antihistaminic drugs are of little value in anaphylactic shock in the mouse, whereas lysergic acid diethylamide gives protection.[111] Monamine oxidase is the enzyme responsible for deactivation of

5-hydroxytryptamine. In fact, 5-hydroxytryptamine may be of importance only in anaphylaxis in rats, mice, guinea pigs and rabbits. Sanyal and West,[90] however, have questioned the importance of both histamine and 5-hydroxytryptamine in the rat.

The role of *acetylcholine* in allergic reactions is still uncertain. Its known physiologic and pharmacologic effects led a number of workers to consider it important. Two studies[47,112] supported this but two other[33,85] experimental studies seemed to refute it. Peters and Silverman[82] in 1946, in a clinical study of a patient, obtained evidence that both histamine and acetylcholine were necessary to cause urticaria. Urbach and Gottlieb[106] in the same year suggested that several biologically active substances are concerned in the allergic reaction. Nakamura[75] has said that his experimental evidence supports the view that acetylcholine is far more important in mediating the anaphylactic reaction than is histamine.

Acetylcholine is found chiefly at nerve endings where it mediates parasympathetic stimulation. It has been suggested that this substance acts by releasing histamine. It has been suggested also that emotionally induced asthma or hives are produced by this chain of events. Acetylcholine is inactivated by the enzyme "cholinesterase."

The *slow-reacting substances* are at present known only by their pharmacologic action. They have been characterized to some extent chemically,[110] but much further study remains to be done before their chemical composition is definitely established.

Two of these substances are of interest to those concerned with the acute allergic reaction: (1) SRS-A, a lipid soluble acid[9,10] and (2) bradykinin, a polypeptide.[110]

The release of a slow-reacting substance in anaphylaxis was first described by Kellaway and Trethewie[58] in 1940 and subsequently has been termed "SRS-A"[9] to indicate its occurrence in anaphylaxis and to distinguish it from other slow-reacting substances. The studies of Brocklehurst[9,10] indicate that SRS-A causes bronchial constriction and that none of the antihistamine drugs counteract its action. It is of most importance in the anaphylactic reactions in man and guinea pigs. Experimental evidence suggests that the activity of Slow-Reacting Substance-A develops as a result of the union of antigen with fixed antibody in the cell. It seems to come from the lung tissue itself and to potentiate the action of histamine by reducing the threshold of histamine response. The enzyme responsible for its inactivation is not known.

Bradykinin was first described by Rocha e Silva and his co-workers[89] in 1949. Subsequently Beraldo[4] showed that it is formed during anaphylactic shock in dogs. Brocklehurst[10] was unable to find evidence of its presence in anaphylactic shock of perfused isolated lungs of guinea pigs or human beings. He further noted that although bradykinin causes the smooth muscle of the gut and uterus of many species to contract, the smooth muscle of the bronchial tree does not respond even to large doses.

The literature on the subject is somewhat confusing because of the number of terms used to designate what is apparently the same substance. A recent article by Lewis[60] adds another term "plasma kinin," to designate vasodilator polypeptides derived from plasma proteins which have bradykinin activity. The importance of this substance or group of substances in the acute allergic reaction in human beings is probably not great on the basis of the evidence at hand.

Hyaluronic acid is one of the best known extracellular substances of connective tissues. Its role, if any, in the allergic reaction is not known. Its presence in the mast cell, however, cannot be ignored.

These chemical mediators, together perhaps with others yet unknown, play parts in the final assault on the blood vessels and the smooth muscle in the shock organs, and thus produce clinically recognizable disease. This review of their functions has been slanted toward their behavior in this type of reaction. They also play a role in other conditions, both normal and stressful. Each substance is inactivated by an enzyme, which is usually found in close proximity to sites of release.

Mention has been made of the variation in response to the anaphylactic reaction in different species and the resistance of the intact rat and mouse to this type of shock. Hence great care must be exercised in transferring data obtained from anaphylactic study of animals to atopic study of human beings. It is probable that certain of the chemical mediators are more important in one species than another.[102]

VARIATIONS IN CLINICAL MANIFESTATIONS OF ALLERGIC REACTIONS

From a diagnostic and therapeutic standpoint, investigators are interested in certain regions of the body, involvement of which causes the clinical syndromes of vasomotor rhinitis, asthma and hives, and some gastrointestinal manifestations of allergy. These regions are therefore mentioned in the diagram (Fig. 1). The nervous system is mentioned chiefly because allergic disease often causes worry and concern on the part of the patient and his family, and because the chronicity of these diseases often makes the patient irritable. The etiologic role of nervous and emotional factors cannot be disregarded,[27] however. This role may be mediated by acetylcholine, as has been indicated already. Dees[21] pointed out that in some cases migraine, epilepsy, meningeal reactions and cranial and peripheral neuritis may be allergic in origin. A primary allergic tension-fatigue syndrome has been well described,[103] but there is no universal agreement as to the frequency of its occurrence.

The reason for the occurrence of asthma in one patient and hives in another, when presumably the same preceding mechanism has taken place in each patient, is not known. It may be due to a variation in end-organ response. Feldberg and Kellaway[36] pointed out that histamine acts locally at the site of liberation and that the symptoms produced may be different from those produced by the injection of histamine into the blood stream.

Dale[16] subsequently suggested the terms "intrinsic liberation" and "extrinsic liberation" of histamine, that is, liberation at the site of action and liberation at a site different from its point of action, respectively. One might wonder, then, whether an overabundance of mast cells is present at the site of reaction in the patient.

The diagram (Fig. 1) of the present knowledge of immediate allergic reaction shows many places where a defect in normal function could lead to abnormal organic behavior. In this respect, the allergic reaction is not unlike the hemophilic diseases which present similar clinical pictures but which have different inherited coagulation defects.[115] The various possible defects may explain why patients vary in clinical manifestation and in response to treatment. Variations in dose of antigen, production of antibody, site of entrance of antigen, kind and site of sensitized cell, type of intracellular enzyme defect, release of chemical mediators, activity and availability of their destroying enzymes, and end-organ response may occur but in various combinations. In other words, the allergic disease may represent a group of inborn errors of metabolism.

PITUITARY-ADRENAL ACTION

Although investigators are concerned chiefly about the effect of adrenocorticotropin and the adrenal cortical hormones used therapeutically, it is well to remember that such hormones are normally present in the body. It is difficult in discussion to separate the physiologic from the therapeutic, though what follows relates more to the therapeutic action of the steroid drugs such as corticotropin (ACTH), cortisone, hydrocortisone and the delta analogues; that is, the gluco-corticoid compounds used in clinical practice at the present time.

These compounds seem to have a threefold effect on the allergic reaction, although undoubtedly there are other kinds of actions that are not now recognized.

1. The antiphlogistic effect is the anti-inflammatory action by which the capillaries are made less permeable.[26] This action occurs at the site of the inflammatory response and is not the result of systemic mechanisms. The greater the inflammation, the larger the dose of steroid necessary to combat it.

2. The effect on production of antibodies is poorly understood. Dixon's[24] work indicates that steroids must be given either before or a few hours after the sensitizing antigen is given if they are to interfere with the production of antibody. Thus the inhibiting effect seems to be on the adaptation phase rather than on the productive phase of antibody formation. Dews and Code[22] showed that in the rat, adrenalectomy enhanced anaphylaxis though not by increasing antibody content of the blood. Yet the administration of cortisone to adrenalectomized rats during sensitization reduced the development of sensitivity. The administration of cortisone to rabbits that were either intact or adrenalectomized, however, lowered great-

ly the resulting concentration of circulating antibody and inhibited the development of cutaneous sensitivity. McMaster and Edwards[68] have shown that antibody-producing organs under the influence of cortisone will take up antigen but will not produce antibody. On cessation of ad-

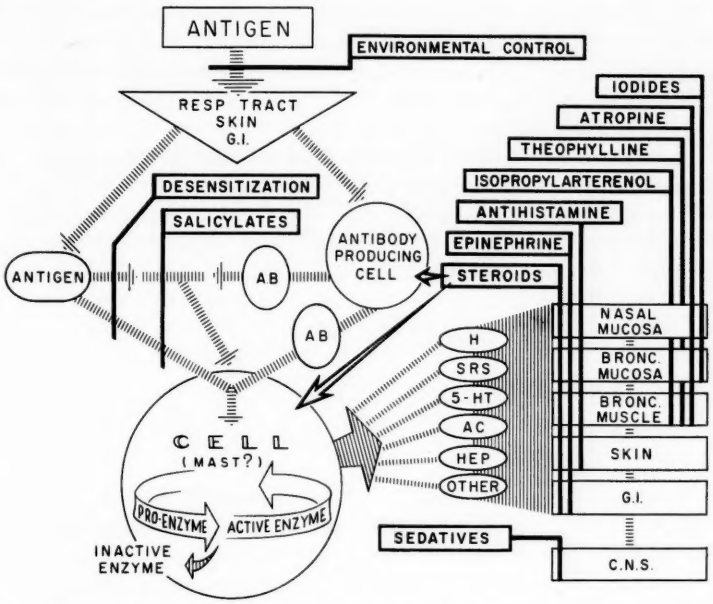

Fig. 2. Representation of the role played by the various forms of treatment used in allergic disease. (From Logan, G. B.: Mechanisms of the immediate allergic reaction and some therapeutic implications. A.M.A. J. Dis. Child., 97:163, 1959.)

ministration of the steroid, the production of antibody begins. Extremely large doses of ACTH or cortisone are required to suppress circulating antibodies,[26] and even when the antibodies are almost suppressed, anaphylactic shock can still occur. In human beings antibody-suppressive doses correspondent to those used in experimental animals are much larger than the doses usually given in clinical medicine.

3. The steroids affect the metabolism of histamine. Schayer[91] and Halpern[48] have shown that cortisone interferes with the biogenesis of histamine in the rat. Skin cells depleted of histamine regain it slowly when the animal is receiving cortisone. Skin cells of adrenalectomized rats that are not receiving cortisone regain histamine rapidly.

Holman and Goth[51] reported that in human beings cortisone did not prevent histamine release by a single injection of a histamine-releasing drug, but it did make the site less responsive to subsequent injections, thus suggesting that human skin may behave like rat skin.

In studies of both adults and children, as judged by urinary studies of histamine,[71] the excretion of free histamine tended to decrease during acute allergic episodes. When steroids were given therapeutically, elimination of free histamine in the urine increased coincidentally with the remission of clinical symptoms.

The favorable effect of the steroids is usually not clinically evident for six to twenty-four hours after their administration. The increase in free histamine in the urine is not evident for twenty-four to thirty-six hours. The urinary excretion of free histamine in normal persons increases slightly during the time they receive steroids.[70]

Clinical experience has demonstrated the value of steroids in the treatment of allergic disease. Much more work remains to be done to explain completely just why they are of value. Further work also must be done to determine the physiologic effects of the pituitary and adrenal hormones on the mechanisms of immunologic reactions.

THERAPEUTIC ASPECTS

Patients having allergic disease must be cared for with presently available and commonly used forms of treatment. The advantages and limitations of each form can be demonstrated best by reference to Figure 2.

Iodides.—The use of potassium or sodium iodide together with moist air and the adequate intake of fluid are important expectorant measures. The dose of iodides must be adequate to produce an effect. Treatment with expectorants is of particular importance for children having asthma.

Atropine.—Theoretically atropine should be a good drug to use in the treatment of asthma. By parasympathetic blocking it produces a bronchodilating action. Atropine or a related drug has been used widely in many medications to treat asthmatic patients. The undesirable drying effect of such a drug on bronchial secretion, however, makes it unsuitable for use in the treatment of asthma in children. It may be of value in conjunction with epinephrine in the treatment of urticaria, as noted by Peters and Silverman.[82] Glaser[42] employed the drug in the treatment of hay fever.

The Theophylline Drugs.—Theophylline and theophylline ethylenediamine are the drugs in this group that are used chiefly in clinical practice. They exert a direct dilating action on bronchial muscle. There is no apparent effect on bronchial or nasal mucosa, though Halpern[49] has credited these drugs with promoting secretion from the bronchial glands because they are vasodilators.

Isopropylarterenol (Aludrine, Isuprel Hydrochloride, Isonorin, Norisodrine).—This drug is used chiefly for its bronchodilating effect. The effect is due seemingly to the sympathomimetic action of the drug, which is considered at present to be the strongest of the bronchodilating agents. For

this reason it is commonly used as the bronchodilating drug when pulmonary function is studied. It is also said to act somewhat as an expectorant.[101]

The Antihistamine Drugs—This chemically heterogeneous group of drugs has many actions in addition to that of competing with histamine for the sites which histamine usually selects for action. It is now well recognized that these drugs do not in any way affect the antigen-antibody reaction or the mechanism by which histamine is released. The drugs must be given in adequate dosage and usually early in the course of the allergic reaction to exert their best effect. They are of no value at all in counteracting the effects of slow-reacting substance, 5-hydroxytryptamine or heparin. Some seem to have an anticholinergic action.[34] It was thought early that diphenhydramine hydrochloride (Benadryl) and tripelennamine hydrochloride (Pyribenzamine) might have some bronchodilating effect. Recent evidence,[92] however, indicates that many of these drugs have a bronchoconstrictive action and that they may serve, under some circumstances, as chemical releasers of histamine.

These drugs effectively compete against histamine in the mucosa of the respiratory tract and in the skin. They do not seem to have any effect against the action of histamine in the gastric secretion.

Epinephrine.—This drug or hormone has both a bronchodilating action and an anti-edema action because of its vasoconstricting effect. These actions are due to a sympathetic stimulating action. Epinephrine is also somewhat antihistaminic in action.

Ephedrine and the various drugs related to it, such as propadrine hydrochloride and pseudoephedrine, have similar actions. There is some evidence that ephedrine acts by suppressing monamine oxidase, which destroys epinephrine.[45]

Sedatives.—The barbiturates and chloral hydrate are frequently employed either alone or in combination with some of the afore-mentioned drugs in the treatment of patients suffering from allergic disease. They have no direct effect on organs concerned in the allergic reaction. The so-called tranquilizer drugs have been used in the treatment of some patients who have chronic or frequently recurrent asthma. It is uncertain whether they do more than help the patient to relax. Chlorpromazine hydrochloride is closely related chemically to promethazine (Phenergan), one of the antihistaminic drugs.

Salicylates.—These substances have been used off and on for years in the treatment of allergic disease. While some of their therapeutic value may be due to their analgesic action, it is possible that there may be some interference with the antigen-antibody union. Some experimental work indicates that salicylates may interfere with production of antibodies and also

with release of histamine and slow-reacting substance when sensitized tissue is exposed to antigens.[105]

Desensitization.—Perhaps a better name for this procedure is "hyposensitization." It seems to have its favorable effect as a result of the production of blocking antibodies in the treated person. These blocking or inhibiting antibodies were first described by Cooke and co-workers[15] in 1935. They seem to act by preventing union of reagin and antigen by uniting with the antigen. The work of Loveless[62] and others has added to the knowledge of the thermostable antibodies. It has been difficult to correlate the titers of blocking antibodies with the clinical course of the patient.[99] It is not known how an antibody in the blood can protect a sensitized cell apparently damaged directly by antigen, as in hay fever.

Environmental Control.—This method, although much discussed, is often poorly understood and therefore frequently inadequately carried out. It is one of the most important therapeutic measures. The most obvious example is transporting a ragweed-sensitive patient to a ragweed-free area during the pollen season. A dust-free or, better stated, dust-poor bedroom is essential in the treatment of patients who are sensitive to house dust. If such a room is properly prepared and meticulously maintained, it is highly effective. Environmental control prevents the antigen from getting into the body of the clinically sensitive child, or at least permits only small amounts to enter the body. The chain of events known as the "immediate allergic reaction" is thereby obviated or minimized.

SUMMARY

A diagram of current knowledge of the mechanism of the acute allergic reaction aids in gaining a better understanding of what is known and what is not known about such reaction. After the antigen enters the body it reaches an antibody-producing cell where reagin formation is stimulated. When the same antigen subsequently enters the body it meets reagin, either in the blood stream or in or on the sensitized cell. Various chemical mediators are released as the result of the antigen-antibody reaction and their action on various end-organs determines the clinical allergic picture. Similarities and differences of the human allergic reaction and animal anaphylaxis are pointed out. The effect of pituitary and adrenal hormones and the most commonly used treatments are shown by fitting their sites of action into the diagram to emphasize their usefulness and limitations.

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Mayo Clinic

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THE PURSUIT OF THE SCIENCE OF MEDICINE

A city that lies exposed to the hot winds—these are those between the winter rising of the sun and its winter setting—when subject to these and sheltered from the north winds, the waters here are plentiful and brackish, and must be near the surface, hot in summer and cold in winter. The heads of the inhabitants are moist and full of phlegm, and their digestive organs are frequently deranged from the phlegm than runs down into them from the head. . . . Children are liable to convulsions and asthma, and to what they think causes the disease of childhood, and to be a sacred disease. Men suffer from dysenterv, diarrhoea, ague, chronic fevers in winter, many attacks of eczema, and from hemorrhoids. Cases of pleurisy, pneumonia, ardent fever, and of diseases considered acute rarely occur. These diseases cannot prevail where the bowels are loose. Inflammations of the eyes occur with running but are not serious; they are of short duration, unless a general epidemic takes place after a violent change. When they are more than fifty years old, they are paralyzed by catarrhs supervening from the brain, when the sun suddenly strikes their head or they are chilled. These are their endemic diseases, but besides, they are liable to any epidemic disease that prevails through the change of the season.—Hippocrates—"On Airs, Water and Places." Translated by W.H.S. Jones and E. T. Withington. Loeb Classical Library.

RESPIRATORY ALLERGY IN CHILDREN

A Double-Blind Cross-Over Study for Eight Consecutive Months with Two Antihistamines and a Sympathomimetic Drug

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THIS STUDY was undertaken to determine whether two antihistamines and a sympathomimetic drug (Triaminic*) given during an entire respiratory infectious season would reduce the incidence of allergic and infectious illnesses in children with asthma and allergic rhinitis. It was suggested by Nungester's[1] observations that when excessive amounts of mucus in the respiratory tract created by allergens, infections, irritants, emotional upsets, and temperature changes overwhelm the cilia, interference with one of the host's natural defense mechanisms occurs. Mucus has other deleterious effects. For example, gastric mucus of the hog interferes with the defense functions of phagocytic cells[2] and the intracellular destruction of bacteria.[3] In man, nasal mucus collected from normal persons as well as those with sinusitis demonstrated inhibitory effects on complement, particularly C^3 and β lysin. Since C^3 is essential to the properidin system, Berendt and Nungester[4] believed that unphysiological concentrations of mucus might alter humoral resistance reactions.

Triaminic was used because it appeared capable of inhibiting excessive mucus formation and of competing with local histamine, thereby controlling allergic and infectious diseases of the respiratory tract. It contains phenylpropanolamine hydrochloride, pheniramine maleate and pyrilamine maleate. The combining of a sympathomimetic with two antihistamines produces a synergestic effect that enhances the usefulness of the compound and reduces side effects.

MATERIAL AND METHODS

The children were from the Allergy Clinic of the Children's Medical Center and our private practice and had asthma and/or allergic rhinitis. All had a complete allergic survey. This included skin tests which were first performed by the scratch method. If these were negative, intradermal tests were done using the common inhalants and foods. Nasal smears, nasopharyngeal cultures, hemograms, chest and sinus x-rays, and other miscellaneous procedures were obtained whenever indicated at the initial visit. The observation period extended from September 1, 1958 to

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*Triaminic is a trademark of the Smith-Dorsey Division of The Wander Company, whose grant aided this study.

April 30, 1959, because these months correspond to that part of the year in Dallas when there is the greatest incidence of respiratory and allergic disorders. From only those children whose past records showed frequent respiratory difficulties of either an infectious or allergic nature, there were chosen at random forty-six for Group A and forty-nine for Group B. Group A received the placebo and Group B Triaminic the first four months (period I). During the second four months (period II) Group B used the placebo, and Group A Triaminic.

The preparations, labeled with the code number, were sent directly from the manufacturer. They were so prepared that the nurses, physicians and patients could not distinguish between the placebo and the active drug. The latter is prepared as a syrup or tablet in the following concentrations:

	5 ml syrup contains	1 juvelet tablet
Phenylpropanolamine hydrochloride	12. 5 mg	25 mg
Pheniramine maleate	6.25 mg	12.5 mg
Pyrilamine maleate	6.25 mg	12.5 mg

The tablet contains half of the active principles in its outer portion which are released immediately. The inner core disintegrates about three to four hours later. Forty-five children used the tablets, and thirty-one the syrup. The initial dose was increased to as much as two teaspoonfuls or two tablets four times a day providing these amounts caused no unpleasant reactions. If he did well, the medication was reduced to one or two doses daily.

Ninety-five patients began the study and seventy-six completed it. In general, there was extremely good co-operation from the children and parents. We were aware that some children did not take the medication as regularly as they reported.

All the children received desensitization therapy to various inhalants. Twenty of the children were given stock bacterial respiratory vaccine to supplement the inhalant desensitization therapy. Food elimination, iodides, oral bronchodilators, and antibacterial drugs were used whenever necessary. A few children received short term steroid therapy.

Many of the children were seen every week. Those who were doing well were permitted to come once every two or three weeks. At each visit the interviewer noted the child's health since his last visit. If there was a history to suggest infection or allergic difficulties, a physical examination was performed. Frequently, examinations were conducted if there were no complaints. Four pediatricians observed the children.

Separate forms were used for this study which summarized the child's history, physical findings, skin tests, therapy and progress notes. On the individual child's protocol, the severity and duration of his illnesses were recorded as noted by the parents and the physicians. Infections were categorized as otitis, tonsillitis, cervical adenitis, U.R.I., bronchitis or pneumonia. At times the picture was that of infection with allergic manifestations. To avoid superfluous data, the physicians' findings in the summary were classified as allergic, infectious, or combinations of the two.

TABLE I. DISTRIBUTION OF CHILDREN IN GROUPS A AND B ACCORDING TO AGE, SEX, DISEASE, SKIN REACTIONS TO COMMON ALLERGENS, AND DESENSITIZATION THERAPY

Age in Years	Group	Sex		Diagnosis			Number of Positive Skin Reactors				Desensitization Treatment	
		M	F	Asthma	Asthma plus Allergic Rhinitis	Allergic Rhinitis	Dust	Molds	Pollens	Foods	Inhalants	Inhalants plus Vaccine
1-5	A	6	6	3	7	2	10	12	10	6	6	6
	B	7	5	3	9	0	11	8	8	7	8	4
6-10	A	16	4	3	15	2	17	18	14	5	14	6
	B	10	11	4	15	2	18	18	16	10	19	2
11-14	A	2	2	2	2	0	4	3	3	2	4	0
	B	6	1	0	7	0	8	7	6	1	5	2
Total	A	24	12	8	24	4	31	33	27	13	24	12
	B	23	17	7	31	2	37	33	30	18	32	8
Totals of	A & B	47	29	15	55	6	68	66	57	31	56	20

TABLE II. NUMBER OF ILLNESSES OBSERVED BY PHYSICIANS AND REPORTED BY PARENTS IN THIRTY-SIX CHILDREN OF GROUP A

Period	Medication	No. of Patient Weeks	No. of Clinic Visits	No. of Illnesses Observed by Physicians			No. of Illnesses Reported by Parents		Courses of Antibacterial Drugs
				Allergic Episodes	Infections (Respiratory)	Allergy and Infections	Asthma	Infections	
I	Placebo	599	319	102	22	23	148	45	36
II	Triaminic	559	288	33	20	10	72	28	21

TABLE III. NUMBER OF ILLNESSES OBSERVED BY PHYSICIANS AND REPORTED BY PARENTS IN FORTY CHILDREN OF GROUP B

Period	Medication	No. of Patient Weeks	No. of Clinic Visits	No. of Illnesses Observed by Physicians			No. of Illnesses Reported by Parents		Courses of Antibacterial Drugs
				Allergic Episodes	Infections (Respiratory)	Allergy and Infections	Asthma	Infections	
I	Triaminic	682	368	82	35	9	111	49	35
II	Placebo	619	269	34	20	11	73	40	24

The parents' reports of illnesses were listed either as asthma or infection. The number of courses of antimicrobial drugs was recorded.

The side effects of the drugs were noted. The physicians asked the parent if the child had taken his medication regularly, and how she evaluated the drug. Such specific reactions as listlessness, drowsiness, irritability, anorexia, anxiety, and sleeplessness were recorded.

Laboratory studies which included nasal smears, cultures, hemograms, urinalysis, and x-rays were performed on a number of patients during the course of the study to determine any adverse effects of the drugs.

Mold and pollen counts were made daily according to accepted standards.[5,6] In addition, Petri dishes were exposed several times a week for mold cultures. These were studied by Dr. M. B. Morrow of Austin, Texas, and by the authors.

RESULTS

The results are presented in the tables. Table I summarizes the distribution of the seventy-six children that completed the study. Thirty-six children are in Group A, and forty in Group B. Twenty-four children are between one and five years of age, forty-one are between six to ten years, and eleven are eleven years of age and older.

Tables II and III show the number of illnesses, allergic and infectious, in each four-month period for both groups. When these tables are compared, it is seen that during period I (September 1-December 31, 1958), there were more allergic and respiratory disorders recorded and more courses of antibacterial agents prescribed than in period II (January 1-April 31, 1959), for both groups regardless of the medication prescribed. This holds true if one notes the observations of the physicians or the reports of the parents.

The data in Tables II and III were statistically analyzed by the chi-square method. If p had a value of less than .05 by this method, it was considered significant because it was quite unlikely that chance alone produced this result. In period I, children receiving Triaminic had a decreased number of physician-observed allergic episodes ($p < .025$). These children also had less combined illnesses observed by physicians and less asthmatic attacks noted by parents. In both of these instances, p was found to be less than .01. For all the other data $p > .05$ and hence was not statistically significant.

Table IV delineates more clearly and simply the results of treatment between the two groups by evaluating the data on the basis of 100 patient weeks. The latter figure was obtained by adding together by groups the total number of weeks that each patient in the group was observed. This total was divided by 100 and the quotient was used to compile the data.

Table V shows that while there was an increased number of visits to the general pediatric clinic in period II, the number of visits to the Allergy Clinic declined and the children in the study had less infectious and allergic illnesses.

TABLE IV. THE NUMBER OF ILLNESSES PER 100 PATIENT WEEKS WITH REFERENCE TO THE MEDICATION ADMINISTERED DURING BOTH PERIODS

Period		I		II	
Medication		Triaminic	Placebo	Triaminic	Placebo
Illnesses observed in the clinic by physicians	Allergic	12.0	18.0	5.9	5.5
	Infectious	5.3	3.7	3.6	3.2
	Allergic and infectious	1.3	3.8	1.8	1.8
Illnesses noted at home by parents	Asthmatic	16.3	24.7	12.9	11.8
	Infectious	7.2	7.5	5.0	6.5

TABLE V. COMPARISON OF THE NUMBERS OF VISITS BETWEEN THE GENERAL PEDIATRIC CLINIC AND THE ALLERGY CLINIC DURING PERIODS I AND II

Period	Number of Visits to General Pediatric Clinic	Number of Visits of All Children to Allergy Clinic	Number of Visits of Children in This Study to Allergy Clinic	Number of Visits of "Sick" Children in This Study to Allergy Clinic
I	11,199	1,207	687	273
II	14,087	1,161	557	128

TABLE VI. TOTAL MOLD AND POLLEN COUNTS FOR EACH PERIOD OF THE STUDY

Period	I	II
Alternaria	1112	938
Other molds	1392	2197
Ragweed	2316	0
Other weeds	127	0
Cedar elm	534	0
Grass	144	541
Mt. cedar	0	1688
Trees	0	2993

Table VI summarizes the number of molds and pollens counted in each period. Plate counts made by Dr. Morrow and ourselves correlate quite closely with the mold counts by the gravity slide method. Dr. Morrow reported that Alternaria, Aspergillus, and Hormodendrum were dominant in the Fall and Spring periods. Penicillium was present in October and November, and in March and April. Pullularia was absent throughout both periods I and II. A few others were noted at various times during the eight months.

Table VII indicates that there were no differences in the number of infectious and allergic respiratory episodes in the children who received inhalant and stock vaccine desensitization and those who were given only inhalant therapy.

There were very few complaints about side effects. Two children stated that both the placebo and the drug made them sleepy and nervous and one said that the drug made him sleepy with two tablets t.i.d., but not with one tablet t.i.d. No abnormal urinary or hematological findings were observed.

DISCUSSION

The most difficult aspect of this study was the evaluation of the patient's complaints. The duration and intensity of all infectious and allergic attacks were recorded on each child's record. Since these did not lend themselves readily to being summarized even if various weights were assigned to the data, each episode reported by the parents, either allergic or infectious, regardless of intensity or duration, was listed as one illness. The patients were examined by experienced physicians who listed the child's illnesses as allergic, infectious, or allergic and infectious. The reports of the parents correlated with the more accurate observations of the physicians. When the number of illnessess observed by them decreased, that reported by the parents decreased to a similar degree. It was felt that the design of the experiment would compensate for these variables. Each group acted as a control for itself as well as for the other group.

Modell and Houde[7] enumerated a number of criteria which they considered necessary for the correct clinical evaluation of a drug. This study adhered to these criteria with the exceptions that the method was not sensitive enough and that forces extraneous to the experiment crept in. In the latter instance, it would seem that we failed to realize that the first four months of study would be a more allergenic period than the second four months. Necessary dependence upon the parents for evaluations of illnesses and for administration of medication decreased the sensitivity of the study.

We are at a loss to explain why the children in both groups had fewer allergic and infectious illnesses in the second half, period II. A survey of the molds and pollens (Table VI) fails to show any striking differences between the two periods. In discussions among allergists from all sections of the country, and in the letters of the International Correspondence Society of Allergists, many theories have been advanced such as "ragweed hangover," marked temperature changes, beginning of school, more house dust, more infections, et cetera. None of these reasons adequately explain this finding. It is our intention to study this more intensively over the next several years. Table V indicates that there was almost a 30 per cent increase in the number of visits to the general pediatric clinic in period II. About 75 per cent of these visits were for treatment of respiratory infections, indicating that there were more respiratory diseases in the months from January 1, to April 30, 1959. In this same period, the number of allergic and infectious illnesses of the children in this study declined by more than 50 per cent.

Antimicrobial agents were administered for only 116 courses to the seventy-six children during the entire eight months. This was very striking when one considered that the children in this experiment were selected because they had many respiratory disorders. The children who received Triaminic took fifty-six courses of anti-infectious drugs, as compared with sixty courses by those taking the placebo over the same length of time.

TABLE VII. COMPARISON OF THE NUMBER OF ILLNESSES BETWEEN CHILDREN RECEIVING VACCINE AND INHALANT DESENSITIZATION AND THOSE RECEIVING ONLY INHALANT DESENSITIZATION

(12 of 36 children in Group A and 8 of 40 children in Group B received vaccine)

Period	Group	Drug	Allergic Episodes		Respiratory Infections		Allergic and Infectious Episodes[1]	
			Inhalants Only	Inhalants and Vaccine	Inhalants Only	Inhalants and Vaccine	Inhalants Only	Inhalants and Vaccine[1]
I	A	Placebo	61	41	16	6	14	9
II	A	Triaminic	21	12	9	11	7	3
I	B	Triaminic	64	18	27	8	7	2
II	B	Placebo	31	3	11	9	10	1

Abernathy, Strem and Good[8] stated their data "fail to confirm the clinical impression that the asthmatic child has far more infections per year than does the normal." However, it seems to us that they were referring to children who received adequate allergic care. In this, we are in complete accord. Allergic children probably are thought to have more infections because their illnesses are more difficult to treat and they have more recurrences, since the initial disease process is not completely eradicated. Often allergic episodes are mistaken for infections. Parents of allergic children are more aware of their child's illness because it frequently leads to asthma.

One other study similar to ours was conducted by Arminio and Sweet.[9] They administered an antihistaminic agent to a group of prisoners during an entire respiratory season. The experiment was well controlled. They reported that the group receiving the antihistamine showed a marked decrease in the number of colds as compared with those taking the placebo. The whole subject of the influence of antihistamines on colds has been critically reviewed.[10,11] We made no attempt to evaluate the effect of Triaminic on the incidence of the common cold.

Stock bacterial respiratory vaccine was administered to those children whose history suggested a large infectious component. It seems from a perusal of Table VII that these children had more allergic and infectious illnesses. Recent well-controlled experiments have demonstrated that vaccine,[12,13] gamma globulin,[8] and prophylactic antibiotics,[14] did not reduce the number of allergic or infectious attacks. The findings of this study concur with Feingold's[15] observations that there is an "absence of the allergic symptoms in the presence of upper respiratory infection when the allergy is under control through treatment, and second, by the decrease in the severity and incidence of upper respiratory infections when the allergy is under control."

Triaminic appeared to have no untoward reactions with the dosage used in the allergic children of this study. It exerted some effect on the allergic process during an highly allergenic period by reducing the number of episodes of asthma and allergic rhinitis without influencing the incidence of infections. Although antihistamines are reported to have a drying effect, this was was not observed by us. Only one child developed pneumonia. We could devise no satisfactory method to measure mucus formation, so that this study did not answer Nungester's question concerning the relationship between excessive mucus and the host's resistance to disease. Perhaps concomitant studies on the properidin system might provide a solution to this intriguing problem.

SUMMARY

Seventy-six children with asthma and allergic rhinitis were observed from September 1, 1958 through April 30, 1959, to evaluate Triaminic in controlling allergic and infectious respiratory episodes. They were placed randomly in one of two groups. The double-blind, cross-over

method was used. At the end of four months, period I was completed and the two groups exchanged the medication.

In period I, there were many more allergic and infectious episodes in both groups regardless of the medication administered. The children receiving Triaminic in this period showed a statistically significant decrease in the number of allergic attacks but had approximately the same number of infections and courses of antibacterial drugs as the controls. In period II, no differences were observed between the groups.

Daily mold and pollen studies showed no essential numerical differences during both periods.

In period II, the allergic children in both groups had a decreased number of respiratory infections while the non-allergic children attending the general pediatric clinic had an increased number.

Stock respiratory bacterial vaccine did not affect the incidence of either infectious or allergic respiratory illnesses.

No untoward effects were observed from the use of Triaminic with the dosage used in these children.

Only 116 courses of antimicrobial agents were administered during the entire study period. Definitive allergic management seems to account for the decreased number of respiratory infections in allergic children.

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INCIDENCE OF ALLERGY IN A PEDIATRIC POPULATION

Pilot Survey of 2,169 Children

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THERE have been many surveys relative to the incidence of allergy. The general opinion is that it approximates 10 per cent of the population as a whole. Rapaport, in his formulation of the Allergic Index[1] suggested, however, that the percentage of major allergy in the over-all population might well be in the area of 15 to 20 per cent. Within recent years there have been several studies referring to the pediatric segment of the population.[2-5] The most recent of these was reported by Crook and his collaborators in 1958.[6] In a group pediatric practice he noted a 14 per cent incidence of major allergy.

The present study,* (sponsored by the Pediatric Committee of The American College of Allergists, Inc.) was projected to arrive at an estimate of the present incidence of major allergy through a sampling of a pediatric population. It is here presented as a continuing project, and is an interval summation of data obtained up to March 10, 1959. The authors limited this study to the following major allergic syndromes: (1) infantile dermatitis (eczema) (under one year of age), (2) seasonal pollinosis, (3) perennial allergic rhinitis, (4) bronchial asthma.

The diagnosis of a major allergy was accepted only when the parent interviewed stated that the diagnosis had been established by a physician. The following allergic manifestations were not included: (1) recurrent upper respiratory infection, (2) urticaria and angioedema, (3) contact dermatitis, (4) food allergy, (5) insect allergy, (6) physical allergy.

The pediatric population was arbitrarily defined as including individuals under the age of fifteen years.

The data presented were obtained from parents by individual or group interviews, using a standardized questionnaire.** The pediatric population was sampled from areas in New York State, Connecticut and the City of Montreal, Canada.† Informants were members of Parent-Teacher Associations, social, philanthropic and other non-medical organizations and in some instances individual parents who were interviewed during the course of home visits by public health nurses. It is evident, therefore,

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ALLERGY SURVEY QUESTIONNAIRE

Indicate "yes" answers with an "X" on line.

1. Are there any allergic illnesses (asthma, hay fever, food allergies) in family?_____

2. How many in family? _____

		Age at 1st Allergic Symptom	Age at 1st Diagnosis
	mother	_____	_____
	father	_____	_____
	#1 sex ____	_____	_____
children	#2 sex ____	_____	_____
	#3 sex ____	_____	_____

3. Did allergic patient have difficulty with infant feeding? _____
Milk used: breast _____ evaporated _____ homogenized _____ milk substitute _____.

4. Did allergic patient have colic _____ rash _____ vomiting _____? Age of onset? _____

5. Did allergic patient have croup _____ croupy cough _____ frequent colds _____ with fever _____
without fever _____? Age of onset _____ which months _____ all year _____?

6. Attacks of sinusitis? _____ frequency _____.

7. Were tonsils and adenoids removed? _____ age _____ month _____ year _____.

8. Did allergic patient have prolonged nasal stuffiness _____ wheezing _____ eye tearing _____ sneezing _____ skin?
rashes _____? Age of onset _____ which months _____ all year _____?
Was the diagnosis made by a doctor? _____ Yes _____ No

9. Was a diagnosis of asthmatic bronchitis made? _____ Age of onset _____ which months _____ all year _____?
Was the diagnosis made by a doctor? _____ Yes _____ No

10. Was a diagnosis of asthma ever made? _____ Age of onset _____ which months _____ all year _____?
Was the diagnosis made by a doctor? _____ Yes _____ No

11. Was a diagnosis of hay fever made? _____ Age of onset _____ which months _____ all year _____?
March ___ April ___ May ___ June ___ July ___ August ___ September ___ October ___.
Was the diagnosis made by a doctor? _____ Yes _____ No

12. Are symptoms associated with dust _____ foods _____ animal pets _____ plants _____ furs _____ cosmetics _____
nervousness _____ dampness _____ medicines _____?

13. Treatment: Medicine by mouth? _____ Injections? _____ Treatment Series? _____ How Long? _____
Result? _____.

We would appreciate any additional comments on the reverse side. Thank you for your cooperation.

Fig. 1

that data have been obtained from a relatively unselected population. None of the information was derived from the case history files of private physicians, out-patient clinics or hospitals.

Granting that there is no completely satisfactory questionnaire, it must be realized that certain omissions (*i.e.* duration and frequency of allergic symptoms, diagnostic procedures, et cetera) had to be made for the sake of expediency. The questionnaire used was one designed by the authors (see Fig. 1).

RESULTS

Data in reference to adults are presented as background and comparative material and further detail in this regard will be forthcoming in a subsequent report.

POPULATION ANALYSIS

Total individuals surveyed 5,152
Total individuals, birth to age 15 years.....2,169
Total individuals, age 15 years and over.....2,983
Total number of families 1,095

ALLERGY INCIDENCE ANALYSIS

Total allergic individuals.....617
(11.97 per cent of total population surveyed)
Birth to 15 years of age.....514
(23.7 per cent of the pediatric population surveyed)
Over 15 years of age.....103
(3.4 per cent of adult population surveyed)

DISTRIBUTION OF ALLERGIC SYNDROMES

BIRTH TO FIFTEEN YEARS OF AGE

Mono-syndromic individuals .....51 per cent
Bi-syndromic individuals .....40.8 per cent
Tri-syndromic individuals ..... 8.2 per cent
Total allergic syndromes.....873
(an average of 2.18 per allergic pediatric individual)
Total in age 15 and over is 209
(an average of .6 per allergic adult)

ALLERGIC ONSET ANALYSIS

Total allergic syndromes.....1,083
(1.75 per allergic individual)
Total syndromes in birth to age 15..... 873
(1.69 per allergic pediatric individual)
Total in age 15 and over group..... 209
(2.0 per allergic individual)
Occurrence of onset of major allergy syndrome:
Birth to age 15.....873 syndromes
Age 15 years and over.....209 syndromes
This indicates that 80.7 per cent of allergic syndromes in this survey start before age 15.

Figure 2 graphically presents the age of onset of major allergic syndromes. It demonstrates that the largest portion of allergic syndromes begin before nine years of age. There is a sharp peak of incidence in the four to nine year age period, during which time 725 syndromes de-

veloped, in contrast to 148 in the next six-year period. This chart also illustrates the significant drop in onset of syndromes after age fifteen. Inasmuch as 873 allergic syndromes of the total 1,082 took onset in

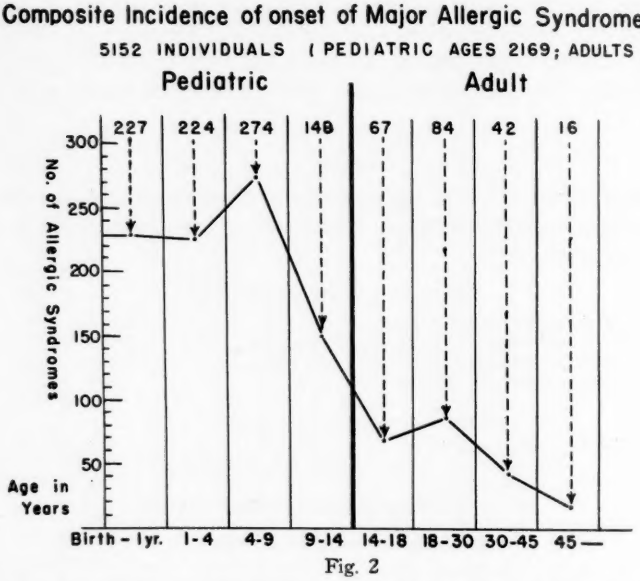

Fig. 2

patients under fifteen years of age, it is seen that 80 per cent of the allergic syndromes in this study took onset during the childhood years.

THERAPY ANALYSIS

Of a total of 741 allergic individuals, only 253 or roughly one third received some form of therapy ranging in type from symptomatic treatment to hyposensitization. In the pediatric group 150 or 37.5 per cent of 400 children with major allergy received therapy and of 341 in the age group over fifteen years of age, 103 or 30.2 per cent were treated.

DISCUSSION

The authors chose to survey samplings of a relatively unselected population because of the opinion previously expressed that the incidence of major allergy is probably higher than that reported in the medical literature. In interviewing the members of lay groups assembled for social or educational activities, it is possible to enumerate both diagnosed and treated allergic persons (those whom the previous reports in the literature encompass), and also those diagnosed and untreated allergic persons who, for the most part, are not included in the literature. Herein may lie the difference in previously and presently reported incidence.

The finding that 80 per cent of the major allergic syndromes take onset

in the pediatric years corroborates well established clinical findings and emphasizes the fact that the roots of allergy are in childhood.

The fact that only one out of three persons suffering with major allergy receives therapy leaves a large segment of persons with a health problem unresolved. One must assume that were the public better informed as to the importance and availability of treatment of allergic disorders, and if the education in medical schools and hospitals were geared to keeping the medical profession aware of the diagnostic facilities available, the percentage of allergic persons receiving treatment would be much higher. There is a practical implication in the fact that approximately two-thirds of the persons with major allergy go untreated. The need is indicated to investigate the relationship of this finding with problems of school and other absenteeism as well as with problems of impaired learning and work efficiency.

The data herewith presented are limited to a survey of a pediatric population in a small area of the northeastern part of this country and apply only to this area. It is hoped that this report will activate similar undertakings in other areas of the country, particularly the mid-western areas where pollen is demonstrated to be a more significant antigenic factor in allergic disease.

CONCLUSION

This survey is based on data obtained by questionnaire in regard to 2,169 children. Of these, 19.54 per cent or roughly, one out of five, had suffered from major allergy.

Furthermore, 80 per cent of the total number of allergic syndromes started under fourteen years of age, indicating that the roots of allergy are in childhood. Only one-third of the individuals with major allergy received treatment.

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A SURVEY OF THE SERUM PROTEIN ELECTROPHORESIS PATTERN IN ALLERGIC CHILDREN

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THE present study is a delineation of the serum protein pattern in a series of 283 allergic children. Serum was obtained when they first presented themselves for an allergy survey. Other tests which were done simultaneously and which are reported here include the blood type, isoagglutinin titre, and degree of skin reactivity to allergens by scratch test. The age, sex, allergic diagnosis and presence of infection are related to the serum protein patterns in order to accumulate some standard of reference for allergic children. Since the gamma globulin fraction has been so intimately related to antibody levels,[1] the levels of gamma globulin are here compared with isoagglutinin levels and skin reactivity.

MATERIAL

The clinical material consists of 283 allergic children from four months to fourteen years of age in whom a definite diagnosis of allergy could be established. The patients were added to the series consecutively, with the only selection being that of an adequate, satisfactory blood specimen. The children presented with the diagnoses as shown in Table I. The distribution of the 170 boys and 113 girls by age is shown in Table II.

A comparison of the sex, age ratio to the incidence of infection in the patients shows a slightly higher percentage of younger girls than boys with infection. Since the total number of patients is small at these ages, this trend may be more apparent than real (Table III).

The serum protein fraction analysis was carried out using the Spinco Model R paper electrophoresis system with a Veronal buffer pH 8.6. The values obtained for serum proteins fractions are shown in Table IV for the 283 children, grouped by age and sex. The mean value for each component, with standard error, and the range of values for each fraction are included, expressed as grams per cent. No specific pattern of serum proteins was evident for allergy in general. The distribution of the values found in this series of allergic children is comparable to that reported for normal children.[2,3] The albumin values obtained in our laboratory are slightly higher than reported by others, and therefore, by comparison the general level of globulin is slightly lower. No differences were found in

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the values for any protein fraction in relation to sex at any age. A further comparison of all the values for each component of the serum proteins in relationship to presence or absence of infection at each age, and for both sexes showed no significant difference (Figs. 1 and 2).

TABLE I. ALLERGIC DIAGNOSES IN 283 CHILDREN

Allergic Rhinitis		193
Alone	52	
+Asthma	117	
+Allergic bronchitis	7	
+Asthma and eczema*	8	
+Eczema*	6	
+G. I. allergy*	3	
	193	
Asthma		185
Alone	51	
+Allergic rhinitis*	117	
+Allergic rhinitis and eczema*	8	
+Eczema*	7	
+Urticaria	1	
+G. I. allergy	1	
	185	
Eczema		39
Alone	18	
+Allergic rhinitis*	6	
+Asthma*	7	
+Asthma and allergic rhinitis*	8	
	39	
Miscellaneous allergic disorders		12
Contact dermatitis	5	
G. I. allergy	2	
Allergic tracheitis	1	
Bacterial allergy	1	
Urticaria	3	
	12	

*Multiple diagnoses per patient.

TABLE II. AGE AND SEX DISTRIBUTION OF 283 ALLERGIC CHILDREN

Age	Males	Females
0 to 12 months	9	1
1 and 2 years	31	22
3, 4, 5 years	66	36
6, 7, 8 years	36	33
9, 10, 11 years	23	16
12, 13, 14 years	5	5
Total	170	113

TABLE III. INCIDENCE OF INFECTION IN 283 ALLERGIC CHILDREN

Age	Males		Females	
	Infected	Non-infected	Infected	Non-infected
0 to 12 months	7	2	1	0
1 and 2 years	18	13	16	6
3, 4, 5 years	25	41	18	18
6, 7, 8 years	15	21	13	20
9, 10, 11 years	5	18	8	9
12, 13, 14 years	2	3	1	4
Total	72	98	56	57

TABLE IV. SERUM PROTEIN VALUES IN 283 ALLERGIC CHILDREN

Age	Sex	No. of Patients	Percentage Total Protein gms.	Percentage Albumin gms.	Globulins			
					Percentage α_1 gms.	Percentage α_2 gms.	Percentage β gms.	Percentage γ gms.
0 to 12 months	M	9	6.5± .06*	4.4± .10	0.3± .02	0.7± .03	0.8± .03	0.4±0.01
			5.2±7.0	2.5—5.3	0.2—0.6	0.4—1.2	0.4—1.4	0.2—0.7
	F	1	6.3	4.7	0.2	0.7	0.7	0.1
1 and 2 years	M	31	6.9± .02	4.4± .03	0.4± .01	0.8± .01	0.8± .01	0.7± .01
			5.9—8.0	2.4—5.8	0.1—1.2	0.5—1.3	0.2—1.9	0.3—1.2
	F	22	6.4± .04	4.2± .15	0.3± .01	0.7± .01	0.7± .01	0.6± .01
			4.6—7.7	2.5—5.2	0.1—0.8	0.4—1.1	0.4—1.2	0.2—1.3
3, 4, 5 years	M	66	6.9± .01	4.5± .01	0.3± .01	0.7± .01	0.7± .01	0.8± .01
			4.2—7.9	2.2—6.0	0.1—0.6	0.4—1.5	0.3—1.2	0.2—1.7
	F	36	7.1± .04	4.6± .02	0.3± .01	0.6± .01	0.7± .01	0.8±0.1
			5.0—8.1	3.1—6.3	0.1—0.6	0.4—1.4	0.4—1.2	0.5—1.4
6, 7, 8 years	M	36	7.1± .02	4.5± .02	0.3± .01	0.7± .01	0.7± .01	0.9± .01
			4.6—8.4	2.3—5.9	0.1—1.4	0.4—1.3	0.4—1.2	0.4—2.2
	F	33	7.0± .30	4.5± .25	0.3± .04	0.6± .06	0.7± .06	0.9± .13
			4.1—8.5	2.6—5.9	0.1—0.5	0.4—1.1	0.3—1.2	0.4—2.0
9, 10, 11 years	M	23	6.9± .04	4.5± .05	0.3± .01	0.6± .01	0.7± .01	0.9± .01
			4.2—7.9	2.4—5.5	0.1—0.6	0.4—1.0	0.2—1.2	0.2—1.7
	F	16	6.7± .07	4.2± .06	0.3± .01	0.6± .01	0.7± .01	1.0± .03
			4.1—8.4	2.8—5.7	0.1—0.6	0.3—1.0	0.5—0.9	0.4—2.1
12, 13, 14 years	M	5	6.8± .14	4.5± .14	0.2± .02	0.7± .07	0.7± .02	0.8± .04
			5.8—7.5	3.5—6.1	0.1—0.4	0.3—1.2	0.5—0.7	0.5—1.1
	F	5	6.8± .14	4.2± .12	0.3± .02	0.6± .10	0.7± .07	1.1± .07
			6.2—7.6	3.4—5.1	0.2—0.3	0.4—0.7	0.4—1.3	0.8—1.5

*Standard Error of Mean.

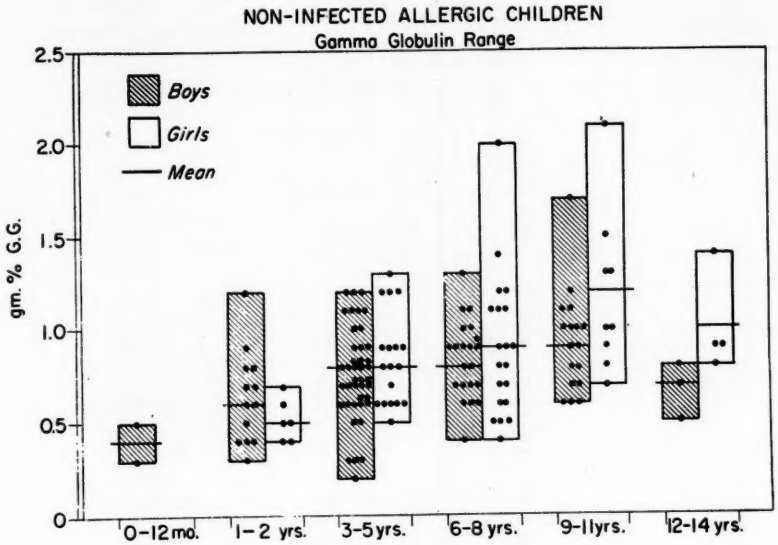
NON-INFECTED ALLERGIC CHILDREN
Gamma Globulin Range
Boys
Girls
Mean
gm. % G.G.
2.5
2.0
1.5
1.0
0.5
0
0-12 mo.
1-2 yrs.
3-5 yrs.
6-8 yrs.
9-11 yrs.
12-14 yrs.

Fig. 1.

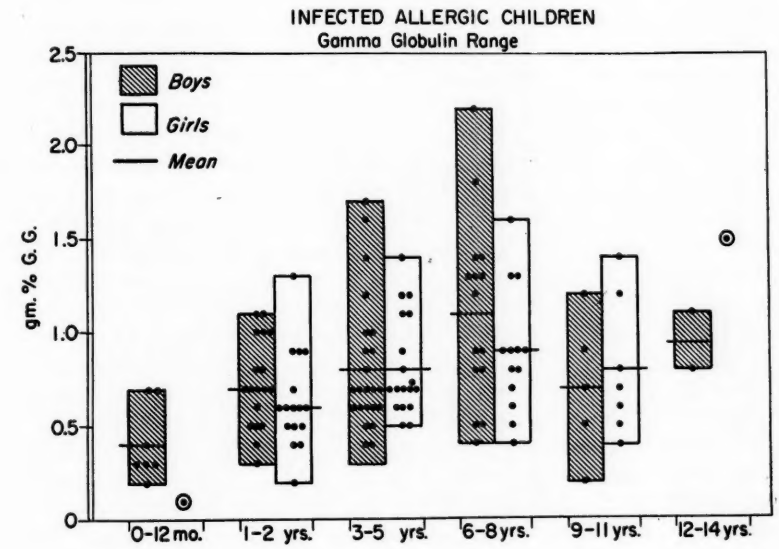
INFECTED ALLERGIC CHILDREN
Gamma Globulin Range
Boys
Girls
Mean
gm. % G. G.
2.5
2.0
1.5
1.0
0.5
0
0-12 mo.
1-2 yrs.
3-5 yrs.
6-8 yrs.
9-11 yrs.
12-14 yrs.

Fig. 2.

TABLE V. SERUM PROTEIN VALUES IN CHILDREN WITH ASTHMA, ALLERGIC RHINITIS AND ECZEMA

Diagnosis	No. of Patients	M/F	Percentages Total Protein gms.	Percentages Albumin gms.	Globulins			
					Percentage α_1 gms.	Percentage α_2 gms.	Percentage β gms.	Percentage γ gms.
Asthma	51	29/22	6.9± .02*	4.4± .02	0.3± .01	0.7± .01	0.7± .01	0.8± .01
			4.6—8.5	2.6—6.0	0.0—1.4	0.3—1.4	0.3—1.2	0.3—2.0
Allergic rhinitis	52	29/23	6.9± .02	4.5± .01	0.3± .01	0.6± .01	0.7± .01	0.8± .01
			4.1—8.1	2.3—6.0	0.1—0.7	0.3—1.2	0.3—1.0	0.2—2.1
Eczema	18	15/3	6.5± .05	3.9± .06	0.4± .02	0.8± .02	0.8± .02	0.7± .02
			4.4—8.4	2.2—5.9	0.1—1.2	0.4—1.5	0.4—1.9	0.2—1.7

*Standard Error of Mean.

The possibility that some differences in serum protein fractions might be found in the various allergic disorders included in our series, prompted a comparison of the values of the fractions in relation to allergic diagnosis. Only those patients with a single allergic disorder are shown in Table V.

TABLE VI. ISOAGGLUTININ TITRE COMPARED WITH GAMMA GLOBULIN LEVEL

Diagnosis	Below 1:32		Above 1:32	
	g.m. Percentage Range	Mean	g.m. Percentage Mean	Range
Allergic rhinitis	0.2—1.0	0.7	0.7	0.3—2.1
Asthma	0.3—1.0	0.6	0.7	0.2—1.5
Asthma and allergic rhinitis	0.5—1.3	0.8	0.8	0.3—2.2
Eczema	0.2—1.7	0.6	0.9	0.8—1.2
Eczema and asthma and/or allergic rhinitis	0.6—0.9	0.7	0.8	0.4—1.2
Group mean		0.7	0.8	

Here again, we find no significant difference between any of the serum components which can be related to a specific allergic disease, and no characteristic pattern for these types of allergy.

At the time this study was started and before some of the simplifications of electrophoretic techniques were available, a simple screening test to detect persons who might have abnormal gamma globulin levels was desirable. The isoagglutinin titre has been proposed as a screening test for the presence of agammaglobulinemia.[4] Based on the assumption that one normally finds some detectable titre, and if this is not demonstrable, there conceivably might be some disturbance in gamma globulin production, it seemed worthwhile to measure the isoagglutinin titres in these children for whom an electrophoretic pattern was obtained. A further assumption was made that persons with isoagglutinin titres lower than 1:32, (a level normally reached within the first few months of life[5]) might have lower than normal gamma globulin. Therefore, a titre of 1:32 was arbitrarily selected as a dividing point, and patients with titres below this level were compared to those with higher values. This comparison of the isoagglutinin titre and the mean gamma globulin, as well as the range of gamma globulin for the various allergic diagnoses, showed no significant differences. In addition, there was no significant alteration in the gamma globulin level in children with isoagglutinin titres above and below 1:32. There was no consistent relationship of titre to age, as some of the very young patients had titres above 1:32, and some of the other children had low isoagglutinins. The titration was not carried out above 1:32, as our interest was in the mere presence of a moderate titre, and not in the ultimate titre (Table VI).

The relationship of the skin tests to the mean gamma globulin level is

shown in Table VII. There is a tendency for the lower gamma globulin values to be associated with the weaker skin reactions, and the slightly higher values with the stronger skin tests. We have the distinct clinical impression that a low normal or lower than normal gamma globulin is more frequently found in children with poorly reacting skins.

TABLE VII. SKIN TESTS RELATED TO GAMMA GLOBULIN

Skin Tests	Gamma Globulin Mean Value gm Percentage				
	Negative	±	+	++	++++—++++
Misc. allergy	.7*	0.4	0.8	0.6*	1.0*
Allergic rhinitis	—	0.5	0.8	0.9	0.9
Asthma	0.8	0.6	0.8	0.8	0.6
Asthma and allergic rhinitis	—	0.7	0.9	0.8	0.8
Eczema	0.6*	0.4	0.2*	0.7	0.9
Eczema, asthma and allergic rhinitis	—	0.6*	0.6	0.8	0.9
Group mean gm percentage		0.5	0.7	0.8	0.8

*Indicates less than three patients, value not included in group mean.

Further clinical characteristics of these allergic children includes a summary of the blood groups encountered. Fifteen per cent were RH negative. The blood groups showed A: 53 per cent, B: 6 per cent, O: 38 per cent, AB: 3 per cent (Table VIII).

DISCUSSION

Since the serum protein electrophoretic patterns obtained from the 283 allergic children who comprise this series are comparable to those of normal children, it would appear that allergic children do not have a characteristic serum protein pattern. These findings are confirmatory of impressions of both Cooke et al[6] and Stroh and Eriksen.[7] We found no sex difference at any age, and although the younger and older age groups consist of only a few patients, the middle periods include as many or more children than have used as a basis for determining published normal values.

Gamma globulin level does not appear to be a decisive factor in allergic children with clinical infection nor in those with a history of repeated infection, although there were some notable instances in which gamma globulin was well below the lower range of normal value. Sixty patients from this series had gamma globulin levels below the mean for their age and have had repeated determinations at intervals of several months. The treatment of a portion of these children with gamma globulin and their infection experience is the subject of a current study.

It was of interest to note the preponderance of boys in the series, and particularly in the three to five-year age group, where they outnumber girls 2 to 1. The observation of a higher ratio of boys to girls with allergy has been commented upon repeatedly, but the significant increase

at this particular age has only recently been stressed.[8] If this proves to be a biological fact it might offer a clue as to the genesis of allergic disorders.

The chance finding of an equal number of children with allergic rhinitis and asthma alone, and twice this number with the combined diagnosis, is also interesting, but the significance of this is not clear. The explanation

TABLE VIII. BLOOD-TYPE DISTRIBUTION IN ALLERGIC AND NORMAL CHILDREN

Type	Rh Positive	Rh Negative	Percentage Total Allergic	Percentage Normal [11]
A	108	15	53	42
B	12	1	6	9
O	72	18	38	44
AB	7	1	3	5
Total	199	35	100%	100%

for the preponderance of asthma alone and combined with allergic rhinitis and other allergic disease, is not surprising since asthma forces itself into attention more dramatically than do some other conditions of a less incapacitating nature.

The youthfulness of the group is worthy of comment since presumably the older allergic child either has adapted to his allergy or because of an increased awareness of allergy, children are being brought for specific diagnosis at an earlier age than a decade ago.

The finding that there is a tendency for the lower gamma globulin values to be associated with weaker allergy skin test reactions is neither meant to imply that the allergy skin tests stem from the level of gamma globulin nor that the skin tests can be substituted for gamma globulin determinations. However, failing to demonstrate clear-cut skin reactions in the absence of any pharmacologic or other reason in a clearly allergic child might lead one to obtain a serum electrophoresis. In this connection, it is interesting to recall the observation of Good and Zak[9] in their study of six agammaglobulinemia patients. These children failed to react with immediate flare and wheal to 114 different allergens, although their skins accepted passive transfer tests, thereby indicating that the skin itself was capable of whealing. These were not allergic children, although some had allergy in the family.

The values obtained for the distribution of blood groups differ from those reported by Abernathy et al[10] for twenty-two allergic children, but are in close agreement with the percents for normal children with which they compare their patients. It is somewhat difficult to determine percentages in a small sample, but no clear-cut preponderance of any blood group seems to occur in allergic children.

SUMMARY

A series of 283 allergic children (170 boys, 113 girls, ages four months through fourteen years) has been studied with serum electrophoresis. No sex difference in serum protein fractions at any age was noted, nor was there any significant difference in the fractions nor in the gamma globulin levels in either infected or noninfected children, nor in those with a history of repeated infection. The general pattern of serum protein was not essentially different from that reported for normal children, and thus no characteristic pattern for allergic children was found.

The isoagglutinin titre and blood groups were unrelated to serum protein levels. The skin test reactivity was suggestively greater in children with higher mean gamma globulin than in those with low levels but this was not a striking difference.

The youthfulness of this unselected group, the preponderance of boys, and the higher ratio of infected to noninfected patients among the girls are trends which may bear further observation.

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A STUDY OF THE NASAL CYTOLOGY IN INFANTS WITH ECZEMOID DERMATITIS

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IT is generally accepted that about 50 per cent of infants with atopic eczema later develop allergic rhinitis or asthma. Others, such as Glaser,[1] report a higher percentage with 80 per cent of his series of infants with atopic eczema subsequently developing allergic respiratory diseases.

Bizzozero[2] in 1887, was the first to demonstrate the presence of eosinophils in nasal mucus, but the credit for stressing the importance of the nasal cytology as a diagnostic tool in allergy belongs to French K. Hansel,[3] who in 1929, stated that nasal eosinophilia was an indication of allergy. Goldman[4] has emphasized that secretions from the nose should be studied from a bacteriological and cytological point of view, just as the cerebrospinal fluid and urine are examined in diseases of the brain and kidneys.

Most authors agree that the finding of local tissue eosinophilia in the nasal secretions is presumptive evidence of allergic respiratory disease.[5,6,7,8,9] Lindsay[10] stated that in patients without allergic rhinitis, the eosinophil count in the nasal secretions was never over 1 per cent. Nasal polyps are generally considered to be associated with allergic rhinitis. Miller[11] reported that in a series of 100 polypectomies, every single polyp contained a marked eosinophilia just below the epithelium, when studied histologically. Kahn,[12] Mansman[13] and Sobel[14] have all concluded that an excess of ten per cent nasal eosinophilia suggests a local antigen-antibody reaction. While others, such as Feinberg,[15] feel that a smaller percentage may be diagnostic of allergic respiratory disease.

Although nasal eosinophilia is considered to strongly indicate an allergic state in the respiratory mucosa, Kelly[16] reported that the excessive use of nasal vasoconstrictors may result in persistent changes in the nasal mucosa accompanied by the presence of eosinophils in the secretions. Matheson[17] has recently reported on nasal eosinophilia in newborn infants. Thirty per cent of 129 normal newborn infants had a nasal eosinophilia in the first four days of life. In most cases when the eosinophilia was present, it persisted for seven to ten weeks. He concluded that nasal eosinophilia is frequent in the first three months of the infant's life and should not be considered abnormal.

Nasal eosinophilia is a finding often associated with respiratory allergy.

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A large per cent of infants and young children with atopic eczema develop allergic rhinitis or asthma. The present study was concerned with the presence of nasal eosinophilia in infants with atopic eczema, seborrheic eczema and contact eczema. A secondary consideration was a two year follow-up in an effort to determine if the nasal cytology in infants and young children with atopic eczema would be an aid in the prediction of the later development of allergic rhinitis or asthma.

MATERIALS AND METHODS

Eighty-five eczematoid infants ranging from five months to twenty-four months of age were studied. The children included in the study were from both private practice and the Pediatric Allergy Clinic of the University of Tennessee. There were forty-one male and forty-four female infants. Any infant with a clinical history or physical findings suggestive of an associated allergic rhinitis or asthma was omitted from the study. A detailed allergic history, physical examination and hemogram were obtained at the first visit. Forty-two of the infants were studied with scratch and intradermal skin tests for the common foods and environmental inhalants. Twelve of the infants in the age group of twelve to twenty-four months were skin tested with pollen extracts because of flare of the eczema during either the weed or grass pollen season.

The eczemoid dermatoses were classified as atopic eczema, seborrheic eczema or contact eczema according to the criteria of Sulzberger,[18] Hill[19] and Glaser.[20] Those children whose eczema could not be classified definitely as atopic, seborrheic or contact, or who appeared to have a mixed type of eczemoid dermatitis, were omitted from the study.

Three serial nasal smears were obtained from all infants for cytological examination. The nasal smears were obtained by use of a soft rubber bulb syringe. Care was taken to insure that the syringe was sterile and dry. The aspirated mucus was transferred to a glass slide and allowed to dry, and then stained by the method of Hansel.[21] The Hansel's stain was applied and allowed to stand for thirty to forty-five seconds, diluted with distilled water for another thirty seconds, and then rinsed with distilled water. The slides were then flooded with 95 per cent ethyl alcohol and again washed with distilled water and allowed to dry. An infant was considered to have a positive nasal eosinophilia when eosinophils were present in clumps or where over ten per cent of the cells in any one of the three specimens. The infants were examined at two to eight week intervals for a two-year period for the development of allergic rhinitis or asthma. There were fifty cases of atopic eczema, twenty cases of seborrheic eczema and fifteen cases of contact eczema in the series. Fifty control infants between six and twenty-four months of age, with no evidence of eczema or other allergic syndromes, were followed in the same way with three initial nasal smears and then again at one to two month intervals for two years.

The recent report by Matheson[17] leads us to survey our newborn popu-

lation for the presence of nasal eosinophils. Fifty newborn infants from the nursery of John Gaston Hospital were studied. Three serial nasal smears were obtained during the newborn period for a cytological study. These newborns had no evidence of any allergic disease and were followed in a special out-patient clinic at two week intervals for five months. On each visit the nasal smears were examined for the cytology.

TABLE I. NASAL EOSINOPHILIA IN NEWBORN INFANTS

Study	Number Studied	Number Positive	Per Cent Positive
Matheson	129	40	30
Crawford	50	13	26

RESULTS

Nasal Eosinophilia in Newborn Infants.

Table I shows that the nasal smears of 26 per cent of fifty normal newborn infants were positive for eosinophils on at least one examination. This compares with a 30 per cent nasal eosinophilia as demonstrated in 129 newborn infants by Matheson. After the nursery period there was a decreasing incidence of nasal eosinophilia in these infants, until at three months, only one infant had a positive nasal smear for eosinophils.

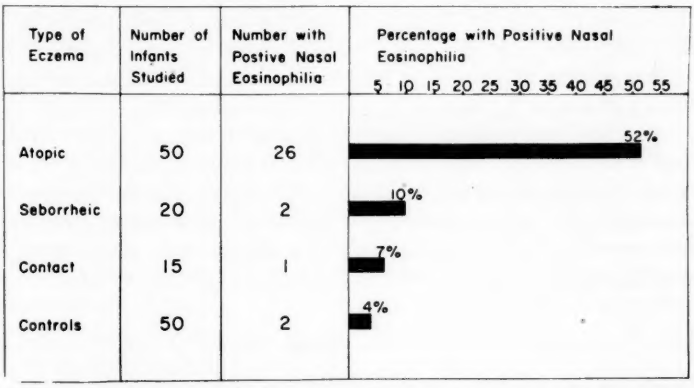

Chart I. Summary of nasal eosinophilia in infants (five to twenty-four months) with various types of eczemoid dermatitis, as compared to control infants (six to twenty-four months).

Nasal Eosinophilia in Infants with Eczema.

Chart I summarizes the percentage of infants with various types of eczemoid dermatitis, whose nasal secretions were positive for eosinophils in at least one of three examinations. A total of twenty-six (52 per cent) of the infants with atopic eczema demonstrated nasal eosinophilia. In contrast, two of twenty (10 per cent) infants with seborrheic eczema, one of

fifteen (7 per cent) with contact eczema, and two of fifty (4 per cent) of the control infants had at least one positive nasal smear for eosinophils.

Progression of Eczema to Respiratory Allergy.

This group of infants was followed periodically for a period of two years after their admission to the study for the development of allergic rhinitis or asthma. None of the children with seborrheic or contact eczema

TABLE II. INFANTS WITH ATOPIC ECZEMA AND CONTROL INFANTS THAT DEVELOPED ALLERGIC RHINITIS OR ASTHMA IN A TWO-YEAR FOLLOW-UP

	Number of Infants	Developed Respiratory Allergy	
		Number	Per Cent
Atopic eczema			
Positive nasal eosinophilia	26	22	85%
Negative nasal eosinophilia	24	9	37%
Controls			
Positive nasal eosinophilia	2	1	50%
Negative nasal eosinophilia	48	1	2%

developed clinical evidence of allergic respiratory disease during this period. Thirty-one (62 per cent) of the fifty infants with atopic eczema progressed to respiratory sensitization, while this was true of only two (4 per cent) of fifty control infants. Table II shows the number and percentage of infants with atopic eczema and control infants who developed allergic rhinitis or asthma in a two-year follow-up. Twenty-two of the twenty-six infants with atopic eczema and positive nasal eosinophilia, or 85 per cent, developed respiratory allergy. On the other hand, nine of the twenty-four infants with atopic eczema and negative nasal eosinophilia, or 37 per cent, progressed to allergic rhinitis or asthma. Two control infants had positive nasal smears for eosinophils and one of these progressed to episodes of asthma associated with bacterial infections. Of the forty-eight control infants with negative nasal eosinophilia, one (2 per cent) developed respiratory allergic disease.

DISCUSSION

There are two fundamental unanswered questions about the eosinophil cell. The exact function and site of formation, whether in the local tissue or bone marrow, remains a controversial subject. The findings in this study in no way add to our basic knowledge of either the function or site of formation of the eosinophil.

The presence of an eosinophilia in the nasal secretions of 26 per cent of infants studied in the newborn nursery compares closely to the 30 per cent reported by Matheson. There was no correlation of the finding of nasal eosinophilia in these newborn infants with any disease syndrome, blood eosinophilia, or type of infant feeding. There was a marked tendency for

the nasal cytology to become negative for eosinophils by two to three months. Nasal eosinophilia in the newborn period would therefore appear to be a normal phenomenon. Eitzman and Smith[22] have demonstrated by use of Rebuck's technique that infants in the neonatal period respond to non-specific inflammation with a marked local eosinophilia. This is in contrast to older children and adults who have been shown by Rebuck[23] to respond to non-specific inflammation by the early migration of neutrophilic leukocytes locally.

The incidence of positive nasal eosinophilia in infants with atopic eczema in our series was 52 per cent. This is considered significant when the incidence of nasal eosinophilia in control infants was four per cent.

The finding of eosinophils in the nasal secretions in infants over three months of age appears to be helpful in classifying an eczemoid dermatitis as allergic or non-allergic.

Sixty-two per cent of the infants that were classified as atopic eczema progressed to a state of respiratory sensitization, during the two-year follow-up. However, 85 per cent of the group with positive nasal smears developed respiratory allergy, as compared to 37 per cent of the infants with atopic eczema and negative nasal smears. In an infant over three months of age with atopic eczema, we consider the finding of nasal eosinophilia of some aid in predicting the later development of allergic rhinitis or asthma. The eosinophil is known to respond specifically to a hypersensitivity reaction and to be specifically attracted to the shock tissue.[24] Our studies would suggest that the eosinophil is attracted to the respiratory shock organ often before the antigen-antibody reaction is of a severe enough degree to be recognized clinically.

SUMMARY

1. Twenty-six per cent of fifty newborn infants were demonstrated to have nasal eosinophilia in the first five days of life. The nasal eosinophilia when present usually disappeared by three months.

2. Twenty-six of fifty infants (52 per cent) with atopic eczema had a positive nasal eosinophilia.

3. Two of twenty infants (10 per cent) with seborrheic eczema had a positive nasal eosinophilia.

4. One of fifteen infants (7 per cent) with contact eczema had a positive nasal eosinophilia.

5. Two of fifty control infants (4 per cent) had a positive nasal eosinophilia.

6. Of the fifty children with atopic eczema, 85 per cent of those with positive nasal eosinophilia developed allergic rhinitis or asthma as compared to 37 per cent of those with negative nasal smears.

7. The finding of a nasal eosinophilia in infants over five months of age is of some value in classifying an eczemoid dermatitis as allergic.

8. The presence of nasal eosinophilia in the group of eczemas studied

was an aid in predicting the later development of allergic rhinitis or asthma.

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MOLD SENSITIVITIES IN ASTHMATIC CHILDREN

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ALLERGIC hypersensitivity to the spores of fungi, molds, rusts, smuts and yeasts has been recognized for thirty years or longer. In 1924 Van Leeuwen[1,2] reported the first cases of mold sensitivity in asthmatic patients in Holland. About the same time, Cadham[3] described asthma due to grain rusts in Canada and Brown,[4,5] Hopkins,[6] Feinberg[7] and other investigators made additional reports.

Rather than being endemic to limited localities, mold spores are widespread. Prince[8] and Durham[9] recorded the incidence of air borne fungus spores in the coastal areas of Texas and throughout the United States. The work of the Association of Allergists for Mycological Investigations, an organization founded by Prince, has greatly increased our knowledge of air-borne fungus spores.

Sensitivity to the spores of fungi is now recognized as an etiologic factor in allergic manifestations.[10,11,12]

STATEMENT OF PROBLEM

Two hundred consecutive cases of bronchial asthma in children in the Chicago area, seen in private practice, were studied in relation to: (1) the age of onset of the asthma; (2) the duration of the asthma when first seen; (3) allergic manifestations in addition to bronchial asthma; (4) mold and other seasonal sensitivities; (5) environmental sensitivities; (6) other sensitivities; (7) the importance of mold sensitivities in the child's total sensitivities, as determined clinically and by scratch and intradermal skin tests, and (8) hyposensitization therapy with mold extracts, as part of general allergic management.

Children whose bronchial asthma begins at an early age and is severe, have multiple sensitivities in various categories of seasonal and environmental inhalants and ingestants.

AGE OF ONSET

Of the 200 children studied, 114 were boys and eighty-six, girls. In 141 patients, the asthma began during the first four years of life; in twenty-six patients it began before one year of age.

In the older children, asthma frequently occurred as a complication of pre-existing perennial and/or seasonal allergic rhinitis.

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DURATION OF ASTHMA

When the patients were first seen, bronchial asthma had been present for a year or less in fifty-four children. In 110, the duration was two to six years; in thirty-three it had been present for seven to ten years, and in sixteen, over ten years.

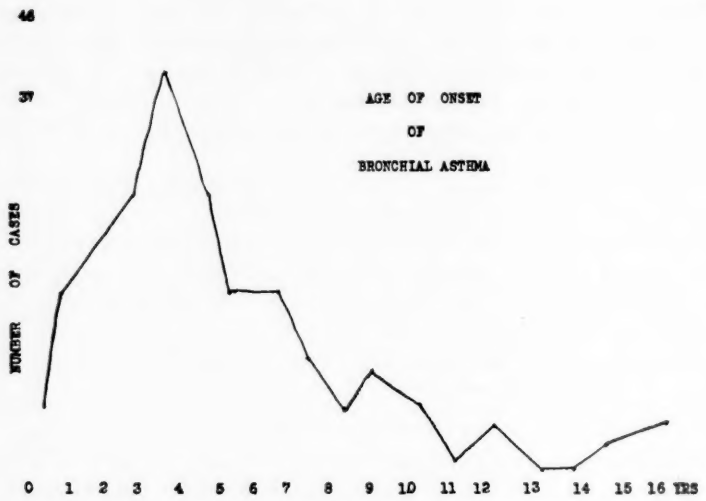

Fig. 1

TABLE I. DURATION OF ASTHMA WHEN FIRST SEEN

Duration	*Number*
< 1 year	54
2 to 6 years	110
7 to 10 years	33
> 10 years	16

OTHER ALLERGIC MANIFESTATIONS

All 200 children suffered from bronchial asthma and many also had other types of allergic manifestations. Thus, sixty-seven had suffered from infantile eczema. In thirteen, atopic dermatitis persisted beyond the age of two.

Perennial allergic rhinitis occurred in ninety-three children and seasonal pollinosis (hay-fever) in fifty-five; eighteen patients had both. Urticaria was present in thirty-seven and angioneurotic edema in six; seventeen children had "croup." Gastro-intestinal upsets, including colic, occurred

in seven children, colitis in two, ulcerative colitis in one child, headaches in three, canker sores in three, vernal catarrh in two, and convulsions in one child from ingestion of pork, while another had anaphylactoid shock from eating nuts.

TABLE II. OTHER ALLERGIC MANIFESTATIONS

Bronchial Asthma	200
Allergic Rhinitis	148
Perennial	93
Seasonal (Hay-fever)	55
Both	18
Atopic Dermatitis	80
Infantile Eczema	67
Beyond 2 years	13
Urticaria	37
Angioneurotic Edema	6
Croup	17
Headaches	3
Gastrointestinal (Including Colic)	7
Canker Sores	3
Vernal Catarrh	2
Colitis	2
Ulcerative	1
Convulsions	1
Anaphylactoid Shock	1

MOLD TESTS

As part of the diagnostic studies all children were tested with the following molds: Alternaria, Hormodendron, Helminthosporium, Cephalosporium, Aspergillus flavus or fumigatus, Penicillium digitatum or rubrum, Chaetomium, Monilia sitophilia, Mucor, Fusarium, Rhizopus and Phoma. Tests for rusts, smuts, and grain mill dust were added for patients from farming areas. One hundred sixty patients were sensitive to mold spores.

OTHER SEASONAL SENSITIVITIES

Only thirty-five patients had mold sensitivity unaccompanied by other seasonal sensitivities; eighteen were sensitive to ragweed alone. Of the 200 children, 160 were sensitive to molds, 135 were sensitive to ragweed, thirty-nine to grass, six to trees, while three had no seasonal sensitivities. Various combinations of seasonal sensitivities occurred to molds, ragweed, grass and trees.

TABLE III. SEASONAL SENSITIVITIES

None	3
Molds	160
Ragweed	146
Grass	39
Trees	6
Ragweed only	18
Molds only	35
Grass only	1

TABLE IV. OTHER SENSITIVITIES

House dust	180
Feathers	155
Animal hairs	126
Orris root	79
Pyrethrum	56
Cottonseed	48
Jute	47
Kapok	42
Tobacco	30

Food sensitivities were also frequent. Markedly positive scratch tests to foods are usually clinically significant. By skin tests and clinically, food sensitivities occurred as shown in Table V.

TABLE V. FOOD SENSITIVITIES

Chocolate	141
Peas and beans	115
Pitted fruits	99
Wheat	91
Nuts	80
Peanuts	66
Tomatoes	57
Citrus fruits	37
Onions	35
Spinach	35
Eggs	30
Vegetable gums	20
Mustard	25
Corn	25
Rice	23
Fish	15
Milk	2

Many other food sensitivities occurred less frequently. Most children had multiple food sensitivities. The combinations of these are being studied and will be reported in a later paper.

MANAGEMENT AND TREATMENT

After a patient's total sensitivities are identified, two procedures are undertaken:

Substances found to be clinically responsible for symptoms are removed from the patient's environment. These include foods. For substances not removable, such as seasonal pollens, mold spores and house dust, specific hyposensitization therapy is instituted. Hyposensitization therapy for mold sensitivity, accompanied by other types of hyposensitization therapy and allergic management was very successful in spite of the long mold season in the Chicago area lasting from early spring until late fall when the ground is not covered by snow.

As hyposensitization therapy for molds, Alternaria or a mixture of mold extracts, either stock or individual was used. The margin of safety between a tolerated dose of mold extract and the production of severe local and constitutional reactions seems to be narrower than with pollen extracts. Each child is tested for his degree of sensitivity to the treatment material employed. Not infrequently, symptoms may be produced by overtreatment with mold extracts.

SUMMARY

1. A high percentage of sensitivity to molds was found in a group of 200 children with bronchial asthma.

2. These children had multiple sensitivities in various categories: seasonal and environmental inhalants, and ingestants.

3. Failure to identify and control mold sensitivity in bronchial asthma may be responsible for failure of allergic management and hyposensitization therapy.

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THE SEARCH FOR TRUTH

From the present peak of scientific achievement the career of science invites a survey of the departures and misemployments on the way. Professor Eric T. Bell comments in the same conviction. Speaking of Pythagoras, he conjectures that if instead of following the lure of that Greek sage, we "had continued along the harsher road of scientific experiment," we should not have had to wait until 1581 for "Galileo to start the scientific age"; and if Archimedes had not been butchered in 212 B.C. but had been accepted as the prime guide instead of Plato, then by 100 A.D. Julius Caesar might have sent the "first and second cruising squadrons of the Roman Air Fleet in a two-hour flight from Ostia (to Athens) with incendiary bombs and cholera germs," and by 300 A.D., "for lack of brains or science to conduct its affairs intelligently, civilization would have ended and *Homo sapiens* returned to its ancestral trees."—JOSEPH JASTROW, *The Story of Human Error,* New York, Appleton-Century Company, 1936.

THE VALUE OF THE LOW DOSAGE METHOD OF HYPOSENSITIZATION THERAPY IN PERENNIAL BRONCHIAL ASTHMA IN CHILDREN

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BECAUSE there exists a difference of opinion[1-6] as to the optimal dosage in hyposensitization therapy of allergic conditions, long-range studies were started in the pediatric allergy clinic of the Strong Memorial Hospital in 1953, to evaluate the various methods recommended in the literature up to that time. A comparative study[7] of the so-called "dilute" or "low dosage" method,[3] the "intermediate dosage" method[4] and the "maximum tolerated dose" method[1] in the treatment of ragweed pollinosis and pollen asthma demonstrated the feasibility of carrying out evaluations of antigen dosage schedules in controlled clinic studies. The present study was subsequently designed to evaluate the "dilute" or "low dosage" method of treatment of perennial bronchial asthma in children.

METHODS

At the start of the experiment the plan was discussed with a statistician who advised on random selection procedures and methods, designed to minimize prejudice in gathering and evaluating the data. The experimental population was drawn entirely from the pediatric allergy clinic of the Strong Memorial Hospital.

After a history was taken, and physical examination and routine laboratory tests and x-rays done, each child with a history of winter asthma was referred from the general pediatric clinic to the pediatric allergy clinic. There the allergy history was reviewed and routine scratch testing to common pollens, molds, epidermoids, foods and miscellaneous vaccines and dust components was performed for each child. Intradermal testing was also done with inhalant allergens to which a child failed to react on scratch testing.

The mother of each child was given advice on avoidance of allergens to which her child reacted on skin testing and on use of symptomatic medications such as antihistaminic agents, sympathomimetic drugs, cough mixtures, et cetera. She was told her child would receive, in addition to symptomatic medication, "allergy injections in the hope that such treatment would increase the child's resistance to contact with allergens." Thereafter each child was assigned by the author to either a "treated group" or a "control group" on the basis of flipping a coin. The exact nature of a child's treatment was not known to his mother or the

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physicians evaluating the child at the end of the study. The author, however, did have this information from the start.

The "treated group" received "hyposensitization" injections of increasing concentrations of mixtures of the inhalant allergens to which he

TABLE I. FREQUENCY DISTRIBUTION OF NUMBERS OF DAYS WHEEZING PER YEAR BEFORE AND AFTER THE STUDY IN THE TREATED AND CONTROL GROUPS

Number Days Wheezing Per Year	Treated Group (Number of Children)		Control Group (Number of Children)	
	Before Study	After Study	Before Study	After Study
More than 70 days per Year	6	4	5	4
50-69 days	4	1	2	0
20-49 days	14	12	17	13
5-19 days	12	16	15	16
0- 4 days	11	14	2	8
Totals		47		41

reacted on testing. The initial dose was 0.10 ml of a 1/10,000,000 weight by volume dilution of antigen in buffered saline. The dose was increased by 0.10 ml each week until an arbitrary "top dose" every twenty-eight days.

The "control group" received a similar dosage schedule, using a sterile buffered saline solution variously labeled to conceal its true identity to all except the author.

The mother of each child was asked to note: (1) number of asthmatic attacks per year, (2) number of days wheezing per year, and (3) number of days school lost due to asthma or complications thereof. She was asked to bring her child to the clinic or emergency room if he developed wheezing or dyspnea, and to note the presence of fever with any asthma he had. She was asked to exclude observations during the grass and ragweed pollen seasons.

Four years after entering the study, the progress of each child was evaluated in terms of number of asthmatic episodes per year, days of wheezing per year, and number of school days missed per year due to asthma. Each child was evaluated by a clinical clerk who did not know to which group the child belonged. The data, thus collected, was then tallied by the author. Of 108 children, between the ages of two and twelve years, and originally placed on the study, adequate follow-up information was obtained on eighty-eight children. The data on these eighty-eight form the basis of this report. Of necessity any conclusions reached in this study resulted from reported observations of mothers. How much subjective bias entered into their reporting is unknown.

RESULT

Table I lists the frequency distribution of the number of days of wheezing per year, in the year before therapy was begun, and the last

year of the study. There were approximately the same number of children in both groups who were severely ill before the study, *i.e.*, who had more than seventy days of wheezing per year. There were somewhat more children in the treated group who were only minimally ill to begin with,

TABLE II. DECREASE IN NUMBERS OF DAYS WHEEZING PER YEAR ACCORDING TO SEVERITY OF ILLNESS BEFORE STUDY

Degree of Improvement		Patients Treated	Controls
	Number of children in each group with more than 70 days wheezing per year before study	5	6
	Improvement in these severely ill children		
Same		3	3
Moderate improvement		1	1
Marked improvement		1	2
	Improvement in the remaining	36	41
Worse		11	9
Same		7	8
1-49%*		11	8
50-99%		7	7
100%		5	9

*Per cent reduction in numbers of days wheezing per year at end of the study.

TABLE III. RELATIONSHIP OF FEVER ASSOCIATED WITH EPISODES BEFORE STUDY AND REDUCTION IN NUMBERS OF DAYS ASTHMA PER YEAR AT END OF STUDY

Reduction in Days Wheezing Per Year	Proportion of Children with Febrile Asthma Episodes Before Study	
	Treated	Controls
More than before study	5/10*	3/6
Same as before study	1/10	6/9
1-49% reduction	4/8	5/11
50-99% reduction	8/10	7/10
100% reduction	1/9	1/5

*The denominator indicates total number of children in each improvement category. The numerator indicates the number of children with febrile asthmatic attacks before the study.

i.e., had less than four days wheezing per year. The frequency distribution for similar information at the end of the study was not significantly different in the two groups.

Table II relates the relative degrees of improvement in reduction in number of days wheezing per year. It deals first with those children in each group who were relatively severely ill to start with and then compares the relative degrees of improvement in the remainder of each group. No significant differences in the results of the two groups can be found in this table.

Table III shows the relationship between the presence of fever with asthma attacks in both groups before the study and reduction in days

of wheezing per year. No significant difference with respect to this detail was found here.

Table IV shows that no significant difference was found in the number of school days lost per year due to asthma. Similarly, an attempt was

TABLE IV. RELATIVE CHANGE IN NUMBERS OF DAYS SCHOOL LOST PER YEAR AT END OF STUDY IN THE TREATED AND CONTROL GROUPS

Change in Number Days School Lost Per Year	Treated	Controls
Same as before study or more	20	12
0-49% reduction	5	1
50-99% reduction	5	5
100% reduction	3	10
Totals*	33	28

*Only children old enough to have attended school at the start of the study are included in this table.

made to correlate clinical improvement with mothers' compliance with dust-proofing advice. Although there were slightly more children in the treated group who showed excellent clinical improvement and whose mothers followed dust-proofing advice, there were also more in the treated group than in the control group who followed dust-proofing advice, and who had more asthma at the end of the study than at the start.

Approximately the same number in each group developed new major allergies during the course of this study. In the control group, four children developed hay fever, four developed perennial allergic rhinitis, and one child developed both these conditions. In the treated group, three developed hay fever, four perennial allergic rhinitis, and three developed both conditions.

Five of the original forty-one in the control group "lost" their original asthma as compared with nine of the forty-seven in the treated group.

At the end of the study, twenty-eight of the control group still wheezed as a result of upper respiratory infections as compared to twenty-five of the treated group. Twenty-three of the control group still had exertional dyspnea at the end of the study as compared to twenty-two of the treated group.

DISCUSSION

It is possible that geographical location may influence the optimum antigen dosage in hyposensitization treatment of perennial asthma just as it apparently does in the treatment of pollinosis.[2] Any conclusions in this report must necessarily apply to only our particular experimental population in Rochester, New York.

With the criteria for comparison used in this study, the results obtained provide no evidence for any difference in the response to the two types

of treatment. Perhaps a larger study, using the same or other criteria of effectiveness might show such a difference.

A certain amount of subjectivity regarding the method of recording and reporting historic facts by the parents undoubtedly "colored" the data. To what degree this influenced the results cannot be evaluated. The most serious difficulty in interpreting the results of this study arises from the fact that the investigator could not avoid knowing to which group each child belonged. This admittedly presented the opportunity for the intrusion of subjective personal bias. In the final analysis, however, the validity of the results rests on the assumption that the investigator's attempt to elicit and record the necessary information, furnished by the externe's interviews with the parents, in an unprejudiced way was successful.

SUMMARY AND CONCLUSION

A single-blind controlled study of the value of the dilute method of hyposensitization of perennial asthma in 108 children in a hospital pediatric allergy clinic is described. A treated group and a control group, both receiving placebo injections of buffered saline, were compared before and at the end of a four year period. When the maximum dose (0.50 ml of a 1/10,000,000 weight by volume dilution of antigenic mixtures) was administered to the children in the treated group every twenty-eight days, no statistically significant differences were observed between the treated and control groups with regard to the following criteria: (1) number of asthmatic episodes per year, (2) average number of days wheezing per year, (3) average number of days school missed per year resulting from asthmatic attacks, and (4) new respiratory allergies developed and original allergic symptoms lost during the study.

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MANAGEMENT OF THE INSTITUTIONALIZED CHILD WITH INTRACTABLE ASTHMA

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THIS PAPER describes what took almost three decades to formulate and to implement the program for the rehabilitation of the children with intractable bronchial asthma.

A child with intractable bronchial asthma is one, who, living in his *own* environment, *fails* to respond to the kinds of formal therapy which relieves or "cures" 90 per cent of all children suffering from bronchial asthma. Thus, about 10 per cent of all asthmatic children suffer from intractable bronchial asthma.

Intractable asthma of childhood is a major allergic illness responsible for many adverse changes in the child's physical being as well as in his psychosomatic make-up. To begin, the child is a seriously sick child with persistent asthmatic breathing difficulty for which he can obtain no relief. Most children with intractable asthma are underweight, restless, irritable, having varying degrees of chronic bronchitis, and are subject to frequent upper respiratory infections. As a result of the persistent asthma, many children develop deformities of the chest as well as chronic emphysema. In addition, many children have a secondary anemia which further saps their vitality. And because of chronic fatigue, irritability, sleeplessness, dyspnea and invalidism, the children all develop emotional defenses against their illness, normal competition with their peers as well as in all of their interpersonal relationships. But the worst thing about intractable asthma of children has been that the outlook for recovery, remission or relief was extraordinarily poor and the doctor could offer no hope that ultimate recovery would take place.

In 1930,[1] I made a plea for a "Home" where children with intractable asthma could be kept for varying periods of time. This was shown to be a humane and therapeutic measure of definite value.

Despite the important clinical findings and personal convictions concerning the basic therapeutic value of separating the child from his own human rather than his physical environment, there was no place to send such children with intractable asthma for as long a period as they might need for full recovery until 1940, when I initiated and established at the nonsectarian Jewish National Home for Asthmatic children at Denver, Colorado, and its recently affiliated Children's Asthma Research Institute and Hospital, a definitive program designed to rehabilitate the child with intractable asthma.

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Each child's application for admission to the "Home" for treatment includes the following components: (a) processing of the application, (b) social and psychological background of the child, and (c) history and physical examination. All applications are requested from and returned to Dr. Samuel C. Bukantz, Medical and Research Director. The only criterion used in the selection of the child is that he has to be truly one who has intractable asthma which resisted the usual forms of treatment in his own community for at least one year. Because the "Home" cannot accommodate all the children with intractable asthma for whom application for admission is made, only the sickest children were selected for admission. It is planned, as a pilot study, to admit children with the earlier stages of intractable asthma, to prevent them from getting the severer or irreversible stage of the disease. In this connection it may be stated that since the advent of corticosteroid therapy, not only has the incidence of intractable asthma in childhood remained unchanged, but the institutional management problem of the children has become more complicated.

To return to the application procedure, it is true that there are many questions contained in the psychological and sociological questionnaire. But these questions are necessary and valuable since they permit a better understanding of the child's life history, his family, his emotional problems and his way of reacting to the emotional factors of his illness. Moreover, it is of importance to learn in detail about the attitude toward placement of the child in the "Home" on the part of the parents and the child.

The application procedure must include a well prepared and meaningful social service report on the family as a whole. For these services help is sought from the various family and child welfare agencies. If the child is to be admitted to the Institute, the agencies help to prepare both the family and the child to accept separation from the home environment. In addition, these agencies continue to help the family through counselling and various levels of psychotherapy while the child is in the "Home" at Denver. Unless the child's parents can develop understanding of their own emotional problems so that they can improve their attitudes and methods of managing their child, the child's intractable asthma may recur upon the child's return to his own home.

In the last two years a number of the Institute's regional medical consultants have participated actively in the processing of the applications. Also, in the last two years Dr. Abramson and I have had the opportunity to study in detail the parental attitudes. This has been implemented by organizing weekly group therapy sessions with the parents of intractable asthmatic children living in the New York area. The findings of this study have been reported.[2]

When accepted for treatment at the Home, children are transported to Denver by airplane. Parents are limited to visits at six-month intervals.

The Home is located on the eastern slope of the Rocky Mountains on a seventeen and one-half acre tract in the western part of the city

of Denver. The location is in a residential district and close to the public schools of the city. Fourteen buildings, including seven cottages for residence of the children, house a total of 150 children. The Home's facilities include a laundry plant, central heating and a well equipped, twenty-bed hospital and a fully equipped clinical laboratory staffed by two full time technicians and a microbiologist. A separate building comprises the dining rooms and kitchens which allows serving the children at one sitting. In addition there is a building for the administrative offices, administrator's cottage and a separate wing of the hospital building housing the psychological services. There is one large recreational field. Not included in the above facilities is a two-story structure devoted entirely to research in allergy.

In each cottage there is one "house parent" for twelve children from twelve to fifteen years of age and one house parent for eight children under twelve years of age. In general, female house parents take care of all girls and the younger boys. Male house parents are provided for the older boys.

Allergy therapy hyposensitization with pollens and molds is given to about 25 per cent of the children and this is carried out in accordance with formal medical practice. Initially, re-evaluation of the allergy state by various methods including skin testing is done. During the first six months of residence anti-allergic treatment is usually withheld in favor of observation. When definite pollen and mold intolerance is established appropriate hyposensitization is instituted. This treatment is effective in contrast to failure of the patient to respond favorably in his own home.

The professional staff is composed of full-time nurses, both registered and practical, ensuring that there are always registered nurses on duty day and night. In addition, there is a dentist, a group of attending physicians including a dermatologist, otolaryngologist and pediatrician, three full-time physicians who are training fellows in allergy, a physical therapist who teaches breathing and other exercises and the medical and research director who is a specialist certified by the American Board of Internal Medicine and Allergy. There is at least one physician in residence at all times. Furthermore, there is a complete staff of local consultants covering every medical and surgical specialty.

Psychotherapy is often the most important phase of the rehabilitation program.

The Home has admitted seven children from the immediate area of Denver and twenty-four children from the areas within the Rocky Mountain region where the climate is quite similar to that of Denver. These children lost their intractable asthma in residence at the Institution. Thus, climate plays a negligible role in the eventual therapeutic results achieved. Even though Denver is a mile high city, the atmospheric pollen and mold concentration nearly always exceeds many areas of the country from which the children originally came.

Statistics covering the results of treatment at the Denver Home and the follow-up study after the children have been returned to their respective families, is the subject of special communications.[3,4]

COMMENT AND CONCLUSIONS

From a practical point of view it was necessary to utilize the fact that the removal of most of the children with intractable asthma to a hospital ward may interrupt the intractability within seventy-two hours. Usually hospitalization maintains the children in a non-threatening as well as a non-allergenic environment. It was also observed both at the local hospital level and at the Denver Home that recurrence of the asthma often coincided with the visits of the parents. Thus, it occurred to me that the relationship with the parents was largely involved in the intractable nature of the asthma and that separation or "parentectomy," a word that I prefer to use because of its psychological implication, led to better results.

The more that was learned of the separation process, the more it appeared that prolonged periods of separation were required and that on the basis of the data obtained at the Home an eighteen to twenty-four month period of separation and treatment was apparently optimal for most of the children. During this period the asthma was treated from the point of view of both soma and psyche. That is, both the emotional problems of the children and their somatic therapies were included in the management procedures. We know to a certain extent what happens to a child in Denver. For example, the condition of group living and the nature of the identification process with the older children leads to a special type of community. This special community is characterized by an interesting development, namely—that the older children often become psychotherapists for the newcomers.

While the child is in Denver, he is taken care of medically, sociologically and psychologically. The child is treated as an individual as well as a member of a group which he is integrated with along many lines, interpersonal relationship to other children, to adults, to school, group play and competitive sports, among other activities. When the child's asthma becomes worse at the Home, I believe this may happen in two major ways. The child may identify the Denver Home with his own home, in which case the child may have to be separated from the Denver Home. In other cases fear of going home was connected with the dangers attendant upon adjusting to school and new friends and probably the parents themselves. Children and the parents especially feared the disruption of a school term.

The impact of a parent's first visit to Denver and subsequent visits which are spaced at six-month intervals, is interesting. The first visit of the parents is usually a threat to both children and parents. This threat decreases during subsequent visits and any asthma occurring during a parent visit decreases as time goes on.[5]

The children have to be carefully prepared for separation from the Denver Home, but nearly all parents were concerned with their own attitudes toward having the children home. Fears of the parents were based on a number of factors.

Thus, the problem of the intractable asthmatic child is a complicated one. Intractable asthma is a condition which occurs in children who have basic immunologic allergies. Environmental tension, which is a product of the reaction of the child to his parents, seems to be the dominating factor in most of the cases. Other factors surely are present. Separation of the child from his own home environment is the prime consideration in the operation of the Denver Home.

The function of the Home in the rehabilitation of children with intractable asthma seems to comprise the following criteria: (1) It offers a haven for the desperately-ill child which allows him to be transferred from his emotionally adverse home environment to an emotionally favorable environment, thus aiding the child to lose those asthmatogenic patterns of psychological reactions which have made his bronchial asthma intractable; (2) It gives the carefully supervised child milieu therapy which allows him to make normal emotional adjustment to his illness, to his peers, and to his parent surrogates; (3) It gives the child whatever antiallergic, medical and specialized psychotherapy he may require to obtain optimal health; (4) It enables the child to respond favorably to specific antiallergic therapy which prior to Denver failed, and (5) It prepares the child emotionally for his eventual return to his own home in a manner which in many instances will prevent the recurrence of the state of intractable asthma. In my opinion, the Denver Home has been fulfilling these five functions admirably.

The whole import of this study is that today we can approach the treatment of the child with intractable asthma with the knowledge that in the vast majority of instances we can help such a child recover from the state of intractable asthma and have him develop either complete freedom from asthma or substantial relief from his condition.

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AN EVALUATION OF HYPOSENSITIZATION IN CHILDHOOD ALLERGY

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ALTHOUGH allergic diseases have been diagnosed and treated since the earliest days of medical science, the subspecialty of allergy has become an entity only within the past fifty years. In more recent years, the pediatrician has been obliged to seek further knowledge in the field of allergy in order to give optimal care to his patients. It has been estimated that allergic children comprise approximately 10 to 20 per cent of the pediatric practice.[1]

Numerous excellent scientific studies have been performed in the field of allergy throughout the years, among which the work of Blackley,[2] von Pirquet,[3] Noon,[4] Schloss,[5] and Cooke[6] stand out. In the past five years, there have been several controlled studies including a placebo study by Frankland and Gorrill,[7] and double-blind placebo studies using autogenous vaccine,[8] gamma globulin,[9] and an extract of Toxicodendron quercifolia.[10] In an extensive review of the literature, including historical reviews of allergy, the authors could find no controlled series studying the relative efficacy of hyposensitization therapy,[11] except in the case of bacterial vaccines.

This paper reports the results of a double-blind placebo study of the effectiveness of hyposensitization in the control of allergic diseases in children.

The number of cases in this study is somewhat small because it is most difficult to accumulate a large volume of carefully standardized patients for a double-blind study. Also, because of the transient nature of a military population, numerous patients were lost to follow-up. It is anticipated that this study will serve as a model for other similar studies and, even though each individual series might contain relatively few cases, in time the total number of cases would be impressive.

PATIENT MATERIAL AND METHODS

The thirty children studied in this series were screened from the general pediatric service at the U. S. Naval Hospital, Jacksonville, Florida. There were nineteen boys and eleven girls, all Caucasian, ranging in age from

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three to fifteen years, with an average age of 8.75 years. The duration of symptoms varied from one to thirteen years, with an average of five years.

The patients selected for this study met at least three of the following four criteria indicating allergic disease: (1) allergic manifestations wit-

TABLE I. FAMILY HISTORY OF ALLERGIC DISEASE

MARKED: Parent(s) and/or Siblings with Allergic History
MODERATE: Siblings of Both Parents with Allergic History
NEGATIVE: Distant or No Relatives with Allergic History

TABLE II. ALLERGENS USED IN ROUTINE SKIN TESTING

(1) Epidermal #1 (EP #1) Cat hair Dog hair Cattle hair Horse hair	(2) Epidermal #2 (EP #2) Goat hair Guinea pig hair Rabbit hair Sheep wool	(3) Mixed Feathers (MF) Chicken feathers Duck feathers Goose feathers Turkey feathers
(4) Mixed Grasses (MG) Bermuda grass Red top grass Johnson grass Blue grass Italian rye grass	(5) Spring Weeds (SW) Red sorrell Lambs' quarters Cockleburr Pig weed	(6) Fall Weeds (FW) Short ragweed Southern ragweed Dog fennell
(7) Mixed Trees (MT) Maple Oak Red cedar Beech Sycamore Palm Sweet gum	(8) Mixed Molds (MM) Hormodendron Alternaria	(9) Mixed Dust (MD) House dust (appropriate for Jacksonville) Upholstery dust Cotton linters
(10) Tobacco Smoke (TS)	(11) Commercial Staph. Vaccine (ST)	(12) Control

Letters in parentheses are abbreviations used in Tables V (a) and VI (a)

nessed by one of the authors, (2) history of allergic disease, (3) nasal eosinophilia, (4) positive family history of allergic disease. If the children met the above criteria and had positive reaction to skin scratch tests, they were included in this study.

The allergic manifestations noted included acute asthma, watering eyes, clear rhinorrhea with "allergic salute," pale and boggy nasal mucous membranes, sneezing, hives, and others. The family history of allergic disease was gauged as to proximity of relationship to the patient (Table I). The nasal eosinophile determinations were performed by the method of Hansel.[12] A modified method of scratch testing for use in a small military installation[13] or in a general pediatric practice (Table II) was employed. The scratch tests were interpreted according to Vaughn and Black.[14]

A double-blind controlled study was set up. The nurse in the pediatric out-patient department selected the children included in the study by odd or even numbers. All children received injections of antigen or the physiologic saline placebo in graded volume. The schedule for increasing hyposentization dosage is noted in Table III.

After eight weeks, all patients were evaluated and graded (Table IV) as to the presence of allergic symptoms. After this evaluation, all patients on the control material were then treated with antigen corresponding to their skin tests and were re-evaluated at the end of eight weeks regardless

TABLE III. ROUTINE HYPOSENSITIZATION SCHEDULE

Dosage	Dilution
1. 0.05 cc.	1:10,000
2. 0.1 cc.	1:10,000
3. 0.3 cc.	1:10,000
4. 0.5 cc.	1:10,000
5. 0.7 cc.	1:10,000
6. 0.1 cc.	1:1,000
7. 0.2 cc.	1:1,000
8. 0.3 cc.	1:1,000

Followed by weekly injections of 0.3 cc. of 1:1,000 mixture.

TABLE IV. EVALUATION OF TREATMENT CLINICALLY

A. No symptoms for eight weeks or more without treatment (symptom-free)
B. Marked decrease in symptoms (improvement)
C. No change
D. Worse since treatment started (worse)

of results on the placebo. All patients were treated as if receiving antigen, which included observation after treatment for untoward reactions. The parents and patients were unaware that a controlled series was being carried out, and the physicians were unaware as to which patients received antigen and which received placebo. All parents were given instructions regarding control of dust, feathers, pollens, et cetera. They also were given a syrup containing phenobarbital 16 mgm, ephedrine 25 mgm, and diphenhydramine 10 mgm per 5.0 cc, to use only if absolutely necessary for abatement of symptoms. This was never given within twenty-four hours before or after a hyposensitization injection, so that the histamine produced by the antibody-antigen reaction was not neutralized by antihistamine. When necessity required treatment of severe allergic symptoms, the injection was omitted for that week. No other medication was given for symptomatic treatment.

RESULTS

Evaluation of the effect of treatment of these allergic patients was based on the clinical impression of the authors, and an appraisal by the parents of their children's conditions compared with that of previous years (Table IV). This evaluation was recorded as the initial results. Those who were originally on placebo treatment were then evaluated after eight weeks on

TABLE V. COMPARISON OF RESULTS IN PATIENTS GIVEN HYPOSENSITIZATION WITH THOSE GIVEN PLACEBO

Series	Total No.	Symptom-Free	Improved	No Change	Worse
Hyposensitization	15	11	4	0	0
Placebo	15	0	4	11	0

TABLE V (a). COMPARISON OF RESULTS IN PATIENTS GIVEN HYPOSENSITIZATION WITH THOSE GIVEN PLACEBO

Summary of Antigens Used*

	Hyposensitization		Placebo
	1. MD, MF, SW		1. SW, FW, MT, MD
	2. MD, MM, MT, EP #1	Improved	2. MD, MM, MF
	3. EP #2, FW		3. MF, MD, SW
	4. MT, MG		4. MG, FW, MD, MF
	5. MD, MF, TS, MT		
Symptom-Free	6. MD, EP #1		5. MF, EP #1, EP #2
	7. FW, SW, MM, MT		6. FW, EP #1, MM
	8. MG, MM		7. MM, MD
	9. MT, MD, EP #2		8. MF, TS, EP #1
	10. MD, MF, EP #1		9. MD, MG, MT
	11. MM, MD, MF, SW, FW, MG		10. MF, EP #1, FW
		No Change	11. EP #1, MM
	12. MM, FW, MT		12. MD, MF
Improved	13. MD, MT, MG, SW		13. MT, MG, FW, SW, MD
	14. MF, MD, EP #2		14. MM, MG
	15. EP #1, MM, MF		15. EP #1, MD, MT, MF

* See Table II for abbreviations.

antigen and recorded again. Thereafter, each child was re-evaluated at monthly intervals for a minimum of thirteen months (average, fifteen months).

Of the fifteen children who received hyposensitization antigen, eleven or 73.3 per cent showed complete abatement of symptoms without the use of symptomatic medication for a minimum of eight weeks and remained symptom-free throughout the period of follow-up (average, fifteen months) (Table V). There were four (26.7 per cent) children who showed a decided improvement. There were no children who were not improved and none who got worse.

Of the fifteen children who received placebo injections, none showed complete suppression of symptoms. Four (26.7 per cent) showed some improvement, but eleven (73.3 per cent) were unchanged. None were worse than before starting the injections (Table V).

No matter how these children responded to the placebo, they were all placed on the hyposensitization schedule following the initial (eight weeks) evaluation (Table VI). Of this group of children, eleven (73.3 per cent) showed complete relief of symptoms on the specific antigen, three (20.0 per cent) showed marked improvement, and one (6.7 per cent) had no change in his condition. No one was worse. In a more thorough evaluation of the children originally on the placebo, a breakdown of the results obtained with the placebo was entertained. Of the eleven children who

TABLE VI. RESULTS OF TREATMENT WITH HYPOSENSITIZATION OR PATIENTS ORIGINALLY GIVEN PLACEBO FOR EIGHT WEEKS

Initial Response	Total Number	Symptom-Free	Improved	No Change	Worse
No change on placebo	11	8	2	1	0
Improved on placebo	4	3	1	0	0

TABLE VI (a). RESULTS OF TREATMENT WITH HYPOSENSITIZATION OF PATIENTS ORIGINALLY GIVEN PLACEBO FOR EIGHT WEEKS

Summary of Antigens Used*

No Change on Placebo		Improved on Placebo	
Symptom-Free	1. MF, EP #1, EP #2 2. FW, EP #1, MM 3. MM, MD 4. MF, TS, EP #1 5. MD, MG, MT 6. MF, EP #1, FW 7. EP #1, MM 8. MD, MF	Symptom-Free	1. SW, FW, MT, MD 2. MD, MM, MF 3. MF, MD, SW
Improved	9. MT, MG, FW, SW, MD 10. MM, MG	Improved	4. MG, FW, MD, MF
No Change	11. EP #1, MD, MT, MF		

* See Table II for abbreviations.

showed no improvement on placebo, eight (72.7 per cent) showed complete suppression of symptoms on the antigen, two (18.1 per cent) showed improvement, and one (9.2 per cent) showed no change. Of the four patients who showed some improvement on placebo, three (75.0 per cent) became completely symptom-free on the antigen, and one (25.0 per cent) showed no further improvement. This demonstrates a statistically significant difference (S.E.D. percentages=1.7 per cent; diff. percentages=43.1). No statistical analyses concerning age, sex, family history, individual skin test results, or nasal eosinophilia were attempted.

DISCUSSION

There is considerable divergence of opinion among physicians in the field of allergy concerning almost every point in allergic practice: some utilize hundreds of allergens in skin testing while others advocate only a few dozen; some use extremely dilute antigens while others use higher concentrations. In this study, rigid standards were set up as to selection of patients, testing, and treatment in order to have a more concrete basis for comparison. There is little doubt that skin testing is a valuable tool in the allergic workup, but, as Peshkin[15] has stressed, it must be carefully and properly evaluated. Occasionally the results of skin tests and clinical allergy do not coincide. Patients who fall into this category were excluded from this study in order to increase the validity of the results.

There are certain very significant differences between childhood and adult allergy.[16] One of the most important differences is that of prognosis.

This may well be that in children the earlier recognition and management of allergic disorders may prevent the severe and irreversible damage often seen in adults. The majority of children with asthma can expect to live essentially normal adult lives if properly managed early. Many children

TABLE VII. OVERALL RESULTS WITH HYPOSENSITIZATION

Total Number	Symptom-Free	Improved	No Change	Worse
30	22(73.3%)	7(23.3%)	1(3.3%)	0(0.00%)

with respiratory allergy have positive skin tests corresponding to their offending allergens. These sensitivities may change, frequently requiring repetition of skin testing, but the results are most rewarding.

The positive effect of the placebo in medicine is well-documented.[17,18] It has also been used successfully in the treatment of allergic disorders[7-10] but to a lesser degree in children. The present study bears out the fact that the placebo does have a moderate effect on some allergic children (26.7 per cent in this series); however, specific hyposensitization is overwhelmingly more valuable in carefully selected children with allergies. The total evaluation of the children of both groups (Table VII), who finally were essentially one group receiving specific hyposensitization inoculations, revealed that, though some of the children had a delay in improvement because of having received the placebo initially, in the final total, a large percentage (73.3 per cent) experienced complete abatement of their allergic symptoms; 23.4 per cent had definite improvement of symptoms, and only one child (3.3 per cent) showed no improvement. This one child, a four-year-old girl, has had sporadic periods of improvement and exacerbations. Her asthma was severely aggravated by an emotionally unstable mother. She would probably benefit greatly by "parentectomy" as practiced at the Jewish National Home for Asthmatic Children at Denver. Another child, who showed only a partial improvement on both placebo and antigen, has been unable to rid his environment of one of his allergens. He is allergic to mixed feathers and three close neighbors raise chickens.

There were two sets of siblings included in the study; one set received antigen and the other set received the placebo. In the final analysis of the twins, three of the four children were completely cleared of symptoms, and the fourth was markedly improved.

The extreme value of controlled studies in all facets of medicine must be stressed. There have been numerous examples where "personal feelings" have guided the profession into principles which later have been found fallacious. However, the present study has demonstrated the therapeutic value of hyposensitization in the treatment of allergy in children.

SUMMARY

1. A double-blind placebo study of the effectiveness of hyposensitization in the control of allergic diseases in children was established.

2. Rigid criteria for selection of patients, testing, and treatment were set up.

3. A statistically significant difference was found between the test and placebo groups.

4. Some of the differences between childhood and adult allergy are mentioned, as is the effect of placebo.

5. The importance of controlled studies is stressed.

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PSYCHOSOMATIC GROUP THERAPY WITH PARENTS OF CHILDREN WITH INTRACTABLE ASTHMA

II. Adaptation Mechanisms

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FOR the past three years we have had the opportunity to discuss with the parents of the children hospitalized in Denver their attitudes toward the rehabilitation program.[1,2] Until we spoke to the parents, we had no idea as to how complex the problem of the adapation of the parents was in terms of giving up their children for about two years. Without studying in detail the transcripts of the verbatim recordings it would be difficult to analyze accurately the frequency of different feelings stemming from the separation. Some of the problems as they have recently developed in the New York area in our parent discussion groups, will be discussed here.

Our parent discussion groups are constructed somewhat the same as Slavson's child-centered group guidance of parents. However, Slavson deals with the parents of normal children. Furthermore, these children are living with their parents. In our parent discussion groups the discussions are "illness-centered" not "child-centered." In addition, the children are 2,000 miles away from home. The parents must adapt not to the children, but to the illness, the letters from the children, the telephone calls, the reports of visitors to the Denver Institution, and other official reports from the Institute. All of these enter into the complex family pattern and are reassembled for the adaptation process of the parents themselves. The parents have to reconstruct their lives in terms of their relationships with the siblings of their child at Denver, his other relatives, such as grandparents, uncles, aunts, friends, the local family physician, as well as the other members and leaders of the parent discussion groups. Most striking of all these, we believe, is the reconstruction which takes place in the parents; that is, the father and mother of any particular child, after attending twenty or thirty group sessions. Our experience runs contrary to that of Slavson.[3] Slavson's child-centered group guidance of parents is governed by the theme that "in the technique with which we are dealing here, attention is focused on the child and the child alone. His nature, his fears, his needs. . ." Slavson emphasizes the need for this form of guidance being completely child-centered and avoiding the personal problems of the parents where these have no direct bearing on those of the children. We feel that it is impossible to deal

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with the relationship of the parents with the intractable asthmatic child without considering the entire interaction of the mother and father of the child as part of the guidance situation. As a matter of fact, many of the couples discuss their relationship with each other quite openly and demonstrate how conflict within the home has intensified the asthmatic process in the child.

One of the more difficult aspects of group psychotherapy is that the procedure requires a transference relationship with the therapist by "self-confrontation" and regression, bringing up matters that ordinarily create both guilt and anxiety. This lengthy process is rapidly catalyzed in our discussion groups by the child's illness leading to a rapid dependency relationship with us. The intensity of this process is so great that painful memories and fears of the parents have often emerged with explosive force in the group sessions. For example, in the past months two of the fathers of children at the Institution wept openly when recalling cruelties they experienced as children at the hands of their own fathers. These emotional vectors feed back into the group and aid in self-confrontation, which is always permitted by the therapist as far as members of the group or ego permit.

One of the most difficult parts of the adaptation process is connected with the compelling need of the parent to fit into his own concept of what the parent's role is. Misconceptions of the role of the parent in child development and the lack of knowledge and understanding of the needs of young children almost invariably lead to a notion of child discipline which embodies punitive measures rather than educational devices. The structured neurotic needs of these parents to strike their children, shout at their children, and deprive their children of commonly accepted rewards, like T.V. and deserts, must be replaced by reconstruction of the ego accompanied by a change in the psyche of both parents. This, of course, involves an important reconstruction of the way in which the parents react upon one another. It may surprise you to hear that we believe that treatment of the parent's relationship with one another is a necessary condition for the successful treatment of intractable asthma in our children at the Institute.

We have commonly observed in our groups that the intractable asthmatic child has become, so to speak, a part of the pattern of the parent's character (chronus complex).[4] This character structure of the parents who have abused their children is the product of culturally determined attitudes which led these parents to relive with their children the patterns of their own childhood. You may recall that "the sins of the parents are carried into the third and fourth generation." We have seen the sins of the parents carried into the third generation in our own groups. Thus, the mother of one of our asthmatic children has had her own mother living with her ever since she was married. This mother acknowledged that she was completely dominated by her own mother and at no time

until she became a member of the group sessions had she ever asserted herself with her own asthmatic child. It was necessary therefore for this mother to give up a pattern of childhood behavior which she had employed up to the age of thirty-five. How successful she will be we do not know. Mothers and fathers exposed to the same cultural and religious forces support one another in their methods of dealing with their asthmatic children. Our parents seem to have been exposed in most instances to cultures believing that "sparing the rod will spoil the child." Razor straps, cat-o-nine-tails, wooden spoons, hair brushes, and belts, amongst other weapons have failed to cure the asthma. One parent said, "What do you expect me to do—sit up and talk to him until three in the morning?" Another parent expressed her rejection of the parental role and stated quite openly in the group session, "Where the children are concerned, I come first." Where there is a strong religious vein in the home the cultural forces are often replaced by spiritual vectors which dominate the interaction of the parents with one another and with their asthmatic child. Where both cultural and religious vectors operate together they seem to synergize one another and prevent the transference relationship from developing. Thus, one couple took the view that the illness of their child was an act of God, that each parent had done the best that he and she could, that they did not see how their attitudes could be changed, and that the beatings the child had received at the hands of the father could not have possibly affected the course of the illness. In contrast to this couple another couple established an excellent relationship with us through an identification process and replaced constant bickering with fruitful discussion between them. They began to project themselves into the nature of their own difficulties and into the needs of their children. The outlook for the second set of parents is good.

One of the most difficult problems in the adaptation of the parents is an error in thinking which has its origins in our culture and that is based upon the belief that when a child's attitude and behavior are so persistent it is believed that children will not change without punitive parental pressure. This fear forces their children to remain in a regressive, somewhat infantile state and interferes with the development of the child both physically and emotionally. At the Institute in Denver the parents know that the independence of the child is encouraged. The parents must adapt to a child who has been subjected not to the neurotic needs of parents to maintain their children at childhood levels, but to demands where every opportunity is given for maturation to proceed uninhibited by parental fears. The way in which parents deal with their anxieties engendered by the Denver Institute is well borne out by two contrasting sets of parents. In one instance the parents "accepted" their healthy child, and perhaps unwisely, discontinued attending the group sessions. They sent us messages that they were so well oriented that they could deal with all the problems that arose, thus rejecting us as

parent figures, and proceeded to manipulate their rehabilitated child's life in their own way. This was also true of a second set of parents, both of whom were highly educated along psychological lines. Surprisingly enough, the mother who stated "I come first" has reversed her role to the pressures placed upon her by the group and by the therapist. She and her husband are reporting in detail the nature of the adaptation process which they are undergoing in dealing with their asthma-free child. The father, however, who is very compulsive, is unable to cope with his healthy child and spent an entire session discussing with the group what measures should be taken to force his eleven-year-old child just recently returned from Denver to hang his clothes away properly. This has become his new problem. One of the difficulties of adaptation of the parents is that the parents, in accord with the way in which adults view current events, always orient their thinking in terms of a cure of their asthmatic children. The asthmatic child is preoccupied with the present. Thus, the asthmatic child gears his parents to sources of anxiety which become more and more intolerable as the intractability of the asthma increases. When the child is removed to Denver the parents are left with the same anxieties, without the source, the asthmatic child, being available. These anxieties, then, are turned toward one another and toward the other children. Not only are their anxieties oriented within their own home but they also extend to the surrogate parents and administrators at the Institute. A good deal of maturity is required to exercise the self-restraint needed to permit the rehabilitation program to proceed. The guilt and anxiety produced by the removal of the child may be intensified by any illness of the child during his stay in Denver. To some parents, a minor cold, ordinarily considered of no consequence in his own home, becomes a major catastrophe while the child is in Denver. A serious illness such as osteomyelitis that recently occurred in one of the children led to the appearance of the parents at the Institute grimly determined to take the child back to their own home in spite of the fact that the child was receiving the best possible medical care for this illness. Fortunately, the parents were persuaded to let the child remain and recover.

One of the more difficult aspects of the reconstruction in the adaptation mechanism required for the successful psychotherapy of the parents, is the realization of parents that their parental instincts are sufficient justification of their attitudes toward their children. Most parents seem to be blindly unaware of the effect of their instinctual drives and the special influences these instincts have from culture to culture. Children are brought up very differently because of the modifications of instinct by religions and cultural needs. The complexities of these adaptation processes seem to be very difficult for the members of our group to incorporate without the aid of supplementary reading. We believe it is important that pressure be brought to bear on the attempts of the parents to reconstruct their attitudes while their children are in Denver. Acting out their feel-

ings with insight is not enough. Understanding the way in which feelings modify attitudes can only be accomplished, however, through techniques which are almost academic in nature. In other words, we believe that these parents have to be told some of the realistic facts as well as develop suitable feelings. The adaptation of the group depends, therefore, on the ability of the parents to deal with abstractions. This is perhaps one of our most difficult stumbling blocks with the rigidly fabricated parent who feels that his parental instinct is sufficient for him to guide the psychosexual development of his intractably asthmatic child.

SUMMARY

Two hundred psychotherapeutic group sessions with parents of intractably asthmatic children hospitalized in Denver are briefly summarized. The parents resided in the area of New York City, with their children, therefore, two thousand miles away. There were always two discussion leaders who co-ordinated both the immunologic and psychologic aspects of the adaptation process required by the parents, connected with the removal of their children to Denver.

The following briefly outlined items are the subject matter of this paper: (1) the "illness-centered" nature of the discussion groups; (2) the effect of communications from the children, visitors, and office reports from the Institute; (3) the effect on sibling relationships, as well as relationships with grandparents and other relatives; (4) the relationship of the parents with one another, incidental to the removal of the asthmatic child; (5) the transference problems with the therapist; (6) the structured neurotic needs of the members of the group, partly with respect to the concept that parental influence must carry punitive authority; (7) the narcissistic needs of the parents; (8) cultural and religious factors; (9) anxiety produced in the parents by attending the group sessions; (10) attitudes toward physical changes in the children while they were in the Denver Institute; and (11) the need for development of insight.

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133 E. 58th (Dr. Abramson)

Submitted July 14, 1959

AN ANALYSIS OF THE EFFECT OF VARIOUS DOSAGE SCHEDULES IN HYPOSENSITIZING PROGRAMS FOR ALLERGIC CHILDREN

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IN A FOLLOW-UP study of 264 allergic children treated in the outpatient allergy clinic of the Hospital for Sick Children, Toronto, there were 279 major diagnoses and 99 minor diagnoses, with a total of 378 diagnoses (Table I). For each diagnosis, an appraisal of response to treatment was made according to the following criteria: The treatment result was considered excellent if there were no symptoms for a six-month period in non-seasonal cases or during the last season implicated in seasonal cases; good if there was considerable improvement; fair if there was only slight improvement; and poor if there was no improvement at all (Table I).

The purpose of this study was to note the effect, if any, of different concentrations of allergens used in the hyposensitizing program for these patients.

METHODS

In every other respect these patients were investigated and treated in an identical manner, that is, with a complete allergic history, physical examination, indicated x-rays and indicated symptomatic therapy with dust-free room precautions, environmental correction, and dietary control, which is considered good treatment for allergic patients. The only way in which the treatment varied at all was when the patients came to clinic they were divided into groups according to the strength of the hyposensitizing solutions which they would receive. This was done in strict numerical order, without regarding the opinion of the examining physician which treatment would be best for a given patient, and without regard to their diagnoses. Some were treated with the so-called high dosage method, and others with the so-called medium-dosage method.

At the time of the onset of the study, all patients in the clinic had been under treatment with the high-dosage method, starting off wih a 1:10,000 dilution of the inhalants and moulds to be included and a 1:20,000 dilution of the pollens (weight per volume). This was worked up as rapidly as possible to a 1:1,000 dilution and then a 1:100 dilution of the inhalants

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and moulds and 1 :2,000 and 1 :200 respectively of the pollens, so that for the greater part of their hyposensitization programs these patients were receiving pollens in a 1 :200 dilution and the inhalants and molds in a 1 :100 dilution. The diluent being used at this time was 7.5 per cent polyvinyl alcohol[5] in normal saline. These patients had all been skin tested, usually with a total of seventy-eight different allergens, approximately half of which were inhalants, pollens and molds, and the remainder foods.

For the purpose of this study, those who were put on the high-dosage schedule had in their extracts from one to twelve inhalants, pollens and molds implicated by history and skin testing, which they were thought to require for adequate hyposensitization. Where only one allergen was used, the initial solution had the inhalants and moulds in a concentration of 1 :10,000 (weight per volume), and pollens in a concentration of 1 :20,000 as before, and these were increased as rapidly as possible to 1 :1,000 and 1 :2,000, then 1 :100 and 1 :200 respectively as before. Because of dilution factors, necessitated by the fact that all solutions were prepared from commercial extracts with inhalants and moulds 1 :10 and pollens 1 :20 dilution, as the number of allergens increased, the concentration of each allergen had to be decreased until a treatment extract containing the maximum of twelve allergens had a final concentration of each inhalant or mould 1 :170 and each pollen 1 :340.

The moderate dosage group received all of the inhalants, pollens, and moulds which were implicated by history and skin tests in a final concentration of 1 :5,000, so that they were not restricted to the twelve most important ones, but received all that were indicated.

Because the high-dosage group had been receiving polyvinyl alcohol as a diluent and we did not wish to change this at the onset of the experiment, the moderate-dosage group was divided, half receiving polyvinyl alcohol as a diluent and half normal saline which is the usual diluent for allergic hyposensitization. Thus there were three groups, all initially of equal size; one on a high-dosage schedule with polyvinyl alcohol as diluent; one on a moderate dosage schedule with polyvinyl alcohol; and one on a moderate-dosage schedule with normal saline.

The high-dosage group was worked up as quickly as possible, usually to 0.5 cc of the strongest solution. The moderate dosage group was worked up only to 0.15 cc and no higher. Regardless of the progress in these cases, there was never any variation in the total dose given, with the exception that if any given dose caused a reaction, subsequent doses were made smaller and increased gradually to the prescribed dose.

In addition, all patients with respiratory allergy received bacterial vaccine, those in the moderate dosage group 0.15 cc of a 1 :10 dilution of stock bacterial vaccine, and those in the high dosage group undiluted vaccine in increasing doses up to 0.5 cc.

TABLE I. ANALYSIS OF TREATMENT RESULTS IN 264 ALLERGIC CHILDREN ACCORDING TO DOSAGE SCHEDULES FOR HYPOSENSITIZING SOLUTIONS

Diagnosis	Total Cases (Number in Brackets Indicates Major Diagnoses)	Treatment Result	Moderate Saline Schedule	Moderate Polyvinyl Alcohol Schedule	Total Moderate Dosage	High Dosage	Per Cent Total Moderate Dosage	Per Cent High Dosage
Asthma	162 (149)	Excellent 72	26	24	50	22	45	44
		Good 69	25	24	49	20	44	40
		Fair 11	2	6	8	3	7	6
		Poor 10	1	4	5	5	4	10
Allergic bronchitis	15 (10)	Excellent 8	3	3	6	2	60	40
		Good 5	1	2	3	2	30	40
		Fair 0	0	0	0	0	0	0
		Poor 2	0	1	1	1	10	20
Perennial allergic rhinitis	98 (61)	Excellent 43	12	10	22	21	36	57
		Good 45	15	16	31	14	51	38
		Fair 0	0	0	0	0	0	0
		Poor 10	5	3	8	2	13	5
Hay fever	45 (32)	Excellent 13	4	7	11	2	36	14
		Good 27	11	6	17	10	55	72
		Fair 2	1	1	2	0	6	0
		Poor 3	1	0	1	2	3	14
Eczema	49 (26)	Excellent 29	9	12	21	8	58	61
		Good 13	6	3	9	4	25	31
		Fair 1	0	1	1	0	3	0
		Poor 6	3	2	5	1	14	8
Miscellaneous	9 (1)	Insufficient cases to analyze.						

RESULTS

At the end of the follow-up period, about two and one-half to three years, it was found that of the 264 cases, eighty-five had been treated by the high-dosage method, ninety-two by the moderate-dosage saline method, and eighty-seven by the moderate-dosage polyvinyl alcohol method, so that the three groups were essentially comparable in numbers for the purpose of follow-up.

The treatment results, both total and according to dosage schedule used, are shown in Table I. Analysis of the figures, particularly the percentage in each category of improvement for each of the diagnoses recorded in the last two columns of the table, shows there is no consistent difference which would indicate an advantage of one dosage schedule over the other. In the case of asthma particularly where most cases were studied and the results are most reliable, the percentages for excellent results, good results, et cetera, are almost identical for each dosage schedule. There is wider variation in those disease entities where there are fewer cases, but these are not considered significant.

However, it must not be concluded from these results that no importance is to be attached to the strength of the hyposensitizing solutions with which the patients are treated. It must be remembered that this was a controlled study where the dosage was not varied even if believed the patient might do better on a different schedule.

During the time of the experiment, one of the authors (C.C-W.) did carry out a completely different form of study on dosage schedules in his private practice. Here all of the patients were started on either a 1:5,000 dilution schedule, or, if considered to be particularly sensitive, they were started on a 1:25,000 dilution schedule, and gradually worked up to a 1:5,000 dilution schedule. All patients were brought up, if possible, to a total dose of 0.15 cc of the solution. If the patient's progress was satisfactory, this concentration of hyposensitizing solution was continued. However, it was found in approximately half the cases that the patients would do much better if variations in the schedule were made.

For example, a considerable number of patients, particularly those with atopic dermatitis, did much better on a more dilute solution, some of them having to go back to 1:1,000,000 dilution. Also some cases of respiratory allergy, particularly asthma, had symptoms with the 1:5,000 dilution and even with the 1:25,000 dilution, and had to be treated with much more dilute solutions, often 1:100,000; although usually it was possible to increase the concentration of their solutions gradually until they eventually reached 1:5,000 dilution. Many of these patients had been treated elsewhere with high-dosage schedules but had experienced such violent reactions that the patient either discontinued taking the injections, or they were discontinued by the physician believing the injections to cause more trouble than the disease itself. Almost always these patients did well on lower-dosage schedules. On the other hand, many patients did better with

more concentrated solutions, particularly with reference to certain allergens. This was especially true with the pollen-sensitive group, and for the most part, those sensitive to ragweed and timothy. These usually had ragweed and/or timothy hayfever with perennial allergic rhinitis the remainder of the year. They did considerably better during the pollen season after receiving higher concentrations of these particular pollens in their hyposensitizing extracts, sometimes as much as twenty or thirty times the amount in the original 1:5,000 dilution. Similarly, many of the dust-sensitive patients did much better with higher than the 1:5,000 concentrations of house dust in their extracts.

The results of this study made in private practice are difficult to analyze statistically because many of these patients had their extracts changed several times. Each time a new extract was ordered a history of their progress was obtained and the extract adjusted accordingly, certain allergens being used in greater concentration or in lower concentration as deduced from the history. Many patients showed dramatic improvement following alterations in their extract.

DISCUSSION

No attempt will be made to review the literature on hyposensitization dosage schedules completely. In brief, there are essentially three schools of thought. The majority of allergists feel that very high concentrations of allergens are necessary. This subject is emphasized by Levin[3] in regard to pollen dosage for pollinosis in children. He reviews the literature with emphasis on those who advocate high doses. The moderate-dosage schedule was advocated by Ratner[4] who had found no need for the high doses which were being used by a great many allergists. Johnstone,[2] in his study on dosage for pollen asthma due to ragweed, found that the high-dosage method and the moderate-dosage method were both quite effective. However, he did not find the very-low-dosage schedule, as championed particularly by Hansel,[1] to be nearly as effective in the ragweed asthma cases.

The authors believe their studies to indicate that not one of these three schools of thought regarding the question of dosage is right. As has been pointed out, patients treated identically from all other points of view and hyposensitized with either the high-dosage or moderate-dosage method of treatment, in general, showed equal progress. Yet, a great many individual patients did better if their dose was lowered considerably, even below the moderate-dosage schedule, and a great many others on the moderate-dosage schedule did better if the concentration of their extract was raised considerably, putting it into the high dosage schedule.

It should be emphasized that the amounts of allergens required in hyposensitization also have a geographic relationship. Some allergens are in much greater concentration in some geographic areas than others, par-

ticularly with reference to the pollens, and, therefore, the dose suitable for a pollen in one area may be considerably different from that in another area. For example, in New York City, the late Dr. Bret Ratner consistently started off with a 1:5,000 dilution of ragweed for ragweed sensitive patients but one of us (C.C-W.) who had found this quite satisfactory in New York City, has discovered that it is frequently too high a dose in the Toronton area where it is often safer to start with a 1:25,000 dilution. Sometimes it is necessary to start with an even greater dilution. Similar generalizations probably apply to various allergens for other geographic areas.

It must be remembered that hyposensitization therapy is only one adjunct in the treatment of these patients and should not be regarded as *the* treatment, as is so often the case. These patients require complete pediatric care other than for their allergies, adequate symptomatic care for their allergies, dietary control, environmental control, control of infection, plus hyposensitization. Any treatment of these patients based on a weekly or bi-weekly "shot" with no regard to the other forms of therapy is completely inadequate treatment.

CONCLUSIONS

It is suggested that instead of keeping rigidly to one dosage schedule for all allergic patients, the doses used at the onset of treatment and the concentrations of the allergens later used be varied according to the progress of the patient. This should be based on a detailed history of relief of symptoms during the particular seasons such as the dust season, the grass season, the ragweed season, et cetera, so that the extract will be tailored to the needs of a given patient without any strict adherence to a preconceived dosage schedule. If this philosophy is followed, results obtained will be much better than when one dosage schedule is rigidly adhered to.

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Editorial

The opinions expressed by the writers of editorials in the ANNALS *do not necessarily represent the group opinion of the Board or of the College.*

THE BIRTH OF ALLERGY

As a friend and collaborator of Clemens von Pirquet, I believe it appropriate that a foreword to an issue dealing with "Pediatric Allergy" should describe how von Pirquet "discovered" allergy. For some time there had been many pertinent observations made which were waiting, so to speak, for the appearance of a genius who, when recognizing their importance, would kindle the spark which would clarify the situation and result in great medical progress.

von Pirquet's interest was aroused by the observation that symptoms of serum-sickness did not appear until after a relatively fixed incubation time. Even the large dose of 200 ccm of scarlatina serum (Moser) used for the treatment of severe cases of scarlet fever was not followed by immediate serum sickness. An incubation time of eight to twelve days elapsed before the first signs of serum sickness appeared. This proved that the serum as such was not toxic. It had to be changed to a toxic substance.

The existence of an incubation time in infectious diseases was well known. The usual explanations of this incubation time were not uniform. In so-called "exotoxic" diseases like diphtheria, it was the time required for the production of enough primary toxin for the development of clinical symptoms of diphtheria.

Another group of diseases, such as smallpox, measles, chickenpox, typhoid fever, and reaction to smallpox vaccination, has a relatively fixed incubation period of eight to fourteen days. This is so constant, in fact, that we can tell in advance when an infected individual will show the first manifestations of the disease. In view of these observations, we assume that the symptoms of such diseases are due to the effect of "endotoxic" substances present within the body of the bacterial agent which is set free by bacteriolytic antibodies produced by the living organism. The explanation therefore of the incubation period in the aforenamed conditions is that the production of these antibodies requires from eight to fourteen days.

These two explanations are not applicable to the incubation period existing in serum sickness, which follows the injection of horse serum or other animal serum into the human organism. Here the incubation period is about eight to twelve days and is relatively fixed, being independent of the amount of serum injected. Serum as such is not toxic. It is a dead

substance and does not multiply. There is no "endotoxin" to be set free.

It was proven that in serum-sickness it was not the antitoxin present in the serum that produced symptoms of the disease, but that it was the horse serum, a foreign protein, that was the cause of the side effects of the therapeutic serum.

Horse serum is a foreign protein which, when introduced subcutaneously, intramuscularly, or intravenously (parenterally) acts as a foreign body, of which the organism must rid itself by destruction. This destruction is carried out in essentially the same manner as that of protein in the gastrointestinal tract, by digestion through ferments. A foreign protein is broken down to peptones, polypeptides and finally to amino acids. Peptone-like intermediary substances are toxic. This toxic phase of digestion is normally quickly passed. The original protein and the amino acids are not toxic. The products belonging to the toxic phase are either not absorbed or they are detoxified by further digestion to amino acids within the intestinal tract or after absorption within the intestinal wall and liver, therefore not damaging the organism. However, while the gastrointestinal tract exists for the purpose of digestion and is prepared for it, the parenteral tissue is not. Ferment-like antibodies capable of digesting the foreign protein must be produced, and this takes time. By interaction of the pathogenic substances of the horse-serum with these antibodies, toxic substances similar to those of the toxic phase of the digestion within the gastrointestinal tract are produced and are responsible for the symptoms of serum sickness.

The question of the incubation time captivated von Pirquet's interest. A child, Egon E., five years old, was admitted with scarlet fever and on October 9, 1903, was injected with 200 ccm of Moser's scarlet fever serum. Seven days later a very severe case of serum sickness set in, lasting over two weeks. The following month, on November 15, 1903, fifteen children, among them Egon, received subcutaneously a prophylactic injection of 1 ccm diphtheria serum in the arm. Eight hours later an intensive swelling of the arm occurred which was followed by fever, lymph gland swelling, and urticaria. von Pirquet noted this observation of a change in the incubation time and directed his studies to other children who received repeated injections of serum. These studies disclosed that such an immediate reaction was a typical response to repeated serum injections. As the serum used in both injections was biologically the same, it was clear that what had changed was the reaction of the organism. It was an immediate reaction to a re-injection of a foreign protein. Furthermore, the reaction was found to be increased in intensity. No bacteria were involved. From further study of similar cases involving re-injections, von Pirquet and I found that if more than four months elapsed between the first and second injections, the symptoms of serum sickness did not appear immediately after the re-injection but four to six days thereafter. In these cases, the incubation time was shortened. We called

this an accelerated reaction. We pointed out that antibodies are responsible for the appearance of serum sickness since the interaction between foreign protein and antibodies changes the foreign protein to a toxic substance.

These antibodies, once produced, do not disappear from the circulation immediately, but only gradually and can be found even three to four months after the first injection. After the antibodies have entirely disappeared, the reactivity of the organism is still altered. The initial injection of horse serum has evidently produced a permanent effect on the cells of the system. We assume that the latter "remember" how to handle the foreign protein, for on re-injection of the serum, antibodies reappear more rapidly than after the initial injection. As long as antibodies are present, the re-injected serum will come in contact with them immediatey. The toxic substances responsible for serum sickness are thus produced immediately and the so-called "immediate reaction" follows. No incubation time is necessary. When antibodies are no longer present, the cells "remember" how to reproduce them more rapidly, and the "accelerated reaction" takes place.

It may therefore be stated that in the light of this theory, the original incubation time is necessary for the production of antibodies. The immediate reaction on re-injection of the pathogenic substance is due to the presence of these antibodies. The accelerated reaction is due to the ability of the cells to manufacture antibodies more rapidly than at the first injection.

von Pirquet realized that the altered reactivity was a fundamental biological fact of great importance. He believed that a new term was needed for the altered reactivity and in 1906 created the term "allergy." He also recognized the diagnostic value of "allergy." An immediate or an accelerated reaction proves that the individual had a previous contact with the pathogenic substance. This finding constituted the starting point for the development of the allergic reaction as a test to prove a previous contact with the same foreign protein, and subsequently to prove a former infection with the infectious agent. The most outstanding was von Pirquet's tuberculin test used as a cutaneous scratch test, later modified by Mantoux to an intracutaneous test for the detection of a previous infection with tuberculosis. Analogous testing was developed for the detection of the causative agents of so-called allergic conditions, such as asthma, hay fever, food allergies, et cetera.

von Pirquet's interest was centered on the study of infectious diseases and immunity. In the first place, he studied smallpox vaccination and later measles. Here, as in all infectious diseases, allergic manifestations follow the same rule. von Pirquet showed that immunity is based on immediate or accelerated reactivity. The presence or rapid mobilization of antibodies kills the invading bacteria, which set free either very small or only moderate amounts of endotoxin, as the invading pathogen microörganism have little time to multiply. Immunity is not due to lack of reaction. To

the contrary, it is due to immediate or accelerated reaction. Many diseases show allergic features. Nephritis, nephrosis, rheumatic infection, collagen diseases, lupus erythematosis, are considered allergic in their pathogenesis and clinical symptoms.

Unfortunately, protein allergy does not lead to immunity. Its treatment consists of desensitization. I call protein allergy a pathologic form of allergy, whereas allergy in infectious diseases is a physiologic form of a life-saving mechanism of nature.

Allergy is not a completely solved medical problem, although much progress has been achieved. A great deal more must still be done. Due to von Pirquet's "discovery" of allergy, the name of von Pirquet is immortal. "Allergy," the term he coined, and von Pirquet belong forever together.

BELA SCHICK

ALLERGY IN CHILDHOOD

That many signs of allergy first appear in childhood can no longer be doubted. In a recently completed survey, the author discovered that almost eighty per cent of the allergic manifestations presented by the patients occurred before the age of fourteen. Although many of these initial symptoms are of minor severity and of only temporary duration, they represent for the skilled allergist a most critical phase, because it is at this point that an accurate diagnosis can lead most readily to successful prophylaxis and effective management of these and other disorders. It is as true of allergy as it is of any other abnormal states that the earlier it is recognized and treatment is initiated, the greater the opportunity for successful results.

Pediatric allergy is a young specialty. Only a few years after the turn of the century von Pirquet developed his tuberculin scratch test and first coined the word "allergy" to define a state of altered response, altered energy, or altered reactivity. It was during this same period that von Pirquet and his friend and co-worker Bela Schick completed their studies in discovering many of the facets of serum sickness. Within the next few years, Schick was to perfect the intradermal test for diphtheria named after him. In 1912 with the introduction of scratch tests with food proteins by Schloss, clinical allergy as we know it today had its beginning. It should be noted that all three of these pioneers in allergy—von Pirquet, Schick, and Schloss—were pediatricians both by training and by practice.

Allergy as a discipline expanded and flourished, and in the latter part of the second decade of the century, clinics devoted to the study and treatment of "altered reactivity" in children began to appear. The first was headed by Peshkin, who has rightly been named "the father of pediatric allergy."

The specialty of pediatric allergy faces many problems. Adequately trained physicians are too few, graduate and undergraduate teaching

facilities are lacking, and equipment and space are often scarce. Sufficient funds for research are not easily available. Perhaps the most important problem is that of attracting young physicians to the specialty of Pediatric Allergy, where there is met day-by-day the ever-changing symptom-reaction complex. Here—all too often, the gratification of therapeutic success is measured in terms of years, rather than days of growth and development.

The problems are complex, but the opportunities are many, and the rewards most gratifying.

HOWARD G. RAPAPORT

WOMEN'S AUXILIARY

Notice of Election of Executive Officers, Governors, and Liaison Officers

In accordance with the Bylaws of the Women's Auxiliary, the Nominating Committee submits herewith the following official slate as approved by the Board of Governors of the Women's Auxiliary of The American College of Allergists, Inc., to be voted upon at the sixth annual business meeting to be held on March 2, 1960, at the Americana Hotel, Bal Harbour, Miami Beach, Florida.

Nominating Committee

MRS. ETHAN ALLAN BROWN, *Chairman*

MRS. STEPHEN D. LOCKEY
MRS. HARRY L. ROGERS
MRS. EUGENE A. SOLOW
MRS. FREDERICK A. STENBUCK

Official Slate

President-Elect	Mrs. Lawrence J .Halpin
Vice President	Mrs. Cecil M. Kohn
Secretary	Mrs. Ralph Hale
Treasurer	Mrs. T. Reed Maxon
Board of Governors (three-year term)	Mrs. Cecil Collins-Williams
	Mrs. M. Murray Peshkin
	Mrs. J. Warrick Thomas*
College Liaison Members (two-year term)†	Dr. Harry L. Rogers
	Dr. Ethan Allan Brown
	Dr. Cecil M. Kohn

Preliminary Program

Tuesday, March 1

10:30 a.m. Executive Committee and Board of Governors Meeting

Wednesday, March 2

9:00 a.m. Registration
10:30 a.m. Sixth Annual Business Meeting
12:30 p.m. Annual Luncheon: Guest Speaker, Dr. M. Murray Peshkin, Past President, ACA

Thursday, March 3

10:30 a.m. Executive Committee and Board of Governors Meeting
3:00 p.m. Presentation of Bela Schick and von Pirquet Awards: Mrs. Maurice Barnes, President of the Auxiliary
7:00 p.m. Banquet

The Auxiliary Hospitality Room will be open for its Sixth Annual Meeting from Sunday, February 28, at 2:00 p.m. until closing time, Friday, March 4.

*According to the Bylaws, Article V, Section 2, *Election:* The retiring President in the year of her retirement shall always be one of the three (3) elected to serve for a three-year term on the Board of Governors.

†According to the Bylaws, Article VII, (e), the three (3) members at large from The American College of Allergists, Inc., serving on the Liaison Committee shall be elected in the even years by the Board of Regents of the College.

Preliminary Program

GRADUATE INSTRUCTIONAL COURSE

February 28—March 1, 1960

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The Americana

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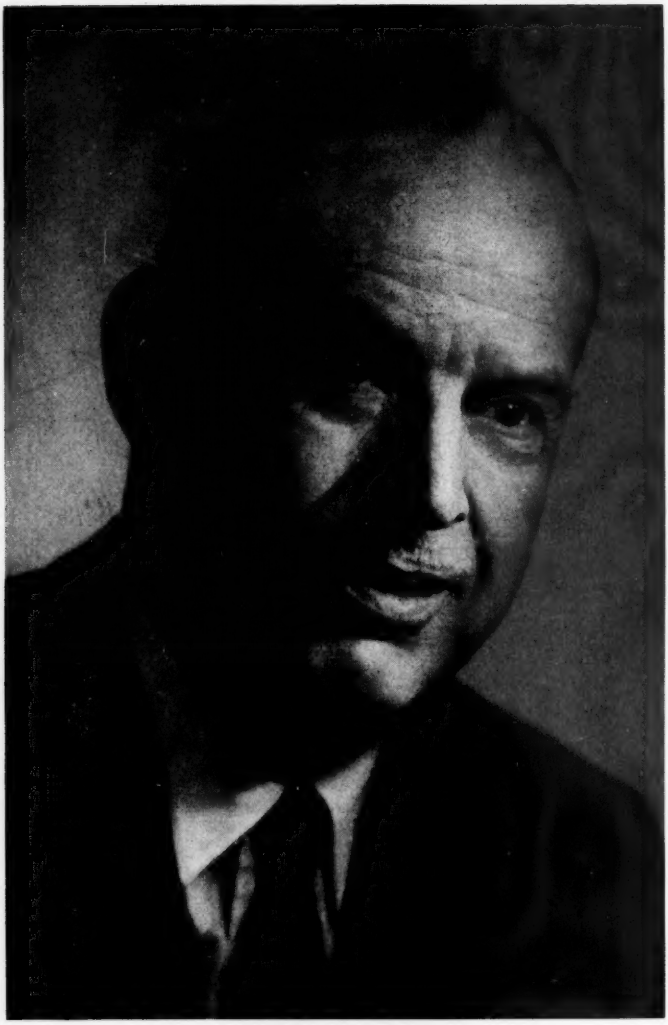

CECIL M. KOHN, M.D.
Kansas City, Missouri
President, 1959-1960

Graduate Instructional Course
The American College of Allergists

(Subject to minor changes)

SATURDAY, FEBRUARY 27, 1960

8:00- 9:00—Registration (Registration also at 8:00-9:00 A.M. each morning)

SUNDAY, FEBRUARY 28, 1960

Theme: Primary Considerations of Some Aspects of the Field of Allergy

Chairman: LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa
Co-Chairman: DELBERT J. PARSONS, M.D., Springfield, Ohio

Morning Session

9:00—Pediatric Respiratory Allergy
GEORGE B. LOGAN, M.D., Mayo Clinic, Rochester, Minnesota

9:45—Contact Dermatitis: Theoretical Considerations
DONALD J. BIRMINGHAM, M.D., Chief Dermatologist, USPHS, Cincinnati, Ohio

10:15—COFFEE BREAK

10:35—First Call to Order

10:40—Second Call to Order

10:45—Allergic Diseases of the Upper Respiratory Tract: Theoretical and Diagnostic Considerations
KENNETH H. HINDEREN, M.D., University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

11:30—Consideration of Skin Tests with Techniques, Evaluations, and Precautions
LEON UNGER, M.D., Northwestern Medical School, Chicago, Illinois

12:00—LUNCH

Afternoon Session

Chairman: KENNETH L. CRAFT, M.D., Indianapolis, Indiana
Co-Chairman: R. DALE DICKSON, M.D., Topeka, Kansas

1:30—Eczematous Allergic Dermatitis: Theoretical and Diagnostic Considerations
ROBERT R. KIERLAND, M.D., Mayo Clinic, Rochester, Minnesota

2:15—Fundamentals of Aerologics
CLIFFORD H. KALB, M.D., Milwaukee, Wisconsin

2:45—Contact Dermatitis: Diagnostic Considerations
DONALD J. BIRMINGHAM, M.D., Chief Dermatologist, USPHS, Cincinnati, Ohio

3:15—RECESS

3:35—First Call to Order

3:40—Second Call to Order

3:45—Allergic Diseases of the Lower Respiratory Tract: Theoretical and Diagnostic Considerations
CHARLES MARPLE, M.D., Director, Allergy Foundation of America, New York, New York

4:30—The Principles of Manufacture of Extracts with Simplified Technique of Preparation
STEPHEN D. LOCKEY, M.D., Chief, Department of Allergy, Lancaster General Hospital, Lancaster, Pennsylvania

Evening Session

First Timer's Get-Together

Chairman: CECIL M. KOHN, M.D., Kansas City, Missouri

8:00—Aims and Ideals of The American College of Allergists
CECIL B. KOHN, M.D., President, Kansas City, Missouri

8:10—Corporate Structure of The American College of Allergists
ELOI BAUERS, Executive Vice-President and Counsel, Minneapolis, Minnesota

8:20—Functions of College Committees
MORRIS A. KAPLAN, M.D., Chicago, Illinois

8:30—Electoral System of The American College of Allergists
LAWRENCE J. HALPIN, M.D., Past President, Cedar Rapids, Iowa

8:40—Types of Fellows—Examination Requirements
G. FREDERICK HIEBER, M.D., Chairman of Credentials Committee, St. Petersburg, Florida

8:50—Annals of Allergy
ETHAN ALLAN BROWN, M.R.C.S. (England), L.R.C.P. (London), Editor, Boston, Massachusetts

9:00—Questions and Answers—ad libitum

MONDAY, FEBRUARY 29, 1960

Theme: Clinical Applications to Present-Day Knowledge in Allergy

Chairman: G. FREDERICK HIEBER, M.D., St. Petersburg, Florida
Co-Chairman: CECIL COLLINS-WILLIAMS, M.D., Toronto, Canada

Morning Session

9:00—Urticaria: Theoretical, Diagnostic, and Therapeutic Considerations
ROBERT R. KIERLAND, M.D., Mayo Clinic, Rochester, Minnesota

9:45—Allergic Diseases of the Upper Respiratory Tract: Therapeutic Considerations
SAM H. SANDERS, M.D., University of Tennessee Medical School, Memphis, Tennessee

10:15—COFFEE BREAK

10:35—First Call to Order

10:40—Second Call to Order

10:45—Contact Dermatitis: Therapeutic Considerations
JOHN L. FROMER, M.D., Lahey Clinic, Boston, Massachusetts

11:15—Allergic Diseases of the Lower Respiratory Tract: Therapeutic Considerations
SOLOMON D. KLOTZ, M.D., Orlando, Florida

11:45—Eczematous Allergic Dermatitis: Therapeutic Considerations
MAURICE C. BARNES, M.D., Waco, Texas

12:15—LUNCH

Afternoon Session

Chairman: HOMER E. PRINCE, M.D., *Crockett, Texas*

Co-Chairman: MAURICE C. BARNES, M.D., Waco, Texas

1:45—Food Allergy
ORVAL R. WITHERS, M.D., University of Kansas Medical School, Kansas City, Missouri

2:15—Nervous System Allergy
LAMAR B. PEACOCK, M.D., Medical College of Georgia, Atlanta, Georgia

2:45—Allergic Headaches
HENRY D. OGDEN, M.D., Louisiana State University Medical School, New Orleans, Louisiana

3:15—RECESS

3:35—First Call to Order

3:40—Second Call to Order

3:45—Physical Allergy
MAYER A. GREEN, M.D., University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

4:15—Allergic Arthritis
JOSEPH HARKAVY, M.D., New York, New York

4:45—Motion Pictures—Titles to be announced

TUESDAY, MARCH 1, 1960

Theme: Progress in Allergy: The Allergist of Today and Tomorrow

Morning Session

Chairman: MAYER A. GREEN, M.D., Pittsburgh, Pennsylvania

Co-Chairman: M. COLEMAN HARRIS, M.D., San Francisco, California

9:00—New Immunological Techniques Useful to the Allergist
LOWELL L. HENDERSON, M.D., Mayo Clinic, Rochester, Minnesota

9:30—Gastro-Intestinal Allergy
PHILIP M. GOTTLIEB, M.D., University of Pennsylvania Medical School, Philadelphia, Pennsylvania

10:00—Use of Antihistaminic Agents
S. WILLIAM SIMON, M.D., Ohio State University College of Medicine, Dayton, Ohio

PRELIMINARY PROGRAM

10:30—COFFEE BREAK

10:50—First Call to Order

10:55—Second Call to Order

11:00—Collagen Diseases
GERALD RODNAN, M.D., University of Pittsburgh Medical School, Pittsburgh, Pennsylvania

11:30—Modern Concepts of Drug Reactions
SAMUEL M. PECK, M.D., New York, New York

12:00—LUNCH

Afternoon Session

Chairman: JOHN H. MITCHELL, M.D., Columbus, Ohio
Co-Chairman: LESTER L. BARTLETT, M.D., Pittsburgh, Pennsylvania

1:30—Clinical Use of Corticosteroids
PHILLIP HENCH, M.D., Emeritus Consultant in Medicine, Mayo Clinic, Rochester, Minnesota

2:15—Enzymes and Allergy
ETHAN ALLAN BROWN, M.R.C.S., (England), L.R.C.P., (London), Director, Asthma Research Foundation, Boston, Massachusetts

2:45—Backgrounds of Immunology
RICHARD T. SMITH, M.D., J. Hillis Miller Health Center, University of Florida Medical School, Gainesville, Florida

3:15—RECESS

3:35—First Call to Order

3:40—Second Call to Order

3:45—Studies in Total Body Irradiation and Attempted Bone Marrow Transplantation
GOULD A. ANDREWS, M.D., Associate Chairman, Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee

4:15—Ocular Allergy
JOHN R. FAIR, M.D., Medical College of Georgia, Augusta, Georgia

4:45—Motion Pictures—Titles to be announced

PRELIMINARY PROGRAM

Sixteenth Annual Congress

WEDNESDAY, MARCH 2, 1960

GENERAL SCIENTIFIC PROGRAM

Morning Session

Chairman: PHILIP M. GOTTLIEB, M.D., Philadelphia, Pennsylvania

Co-Chairman: MARK H. MOTHERSILL, M.D., Indianapolis, Indiana

9:00—Address of Welcome
JAMES H. PUTMAN, M.D., President, Florida Allergy Society, Miami, Florida

9:05—Response
CECIL M. KOHN, M.D., President, The American College of Allergists, Inc., Kansas City, Missouri

9:10—Antigenicity of the Whey Proteins in Evaporated Cow's Milk and Whole Goat's Milk
SIDNEY SAPERSTEIN, Ph.D., Research Laboratories, Pharmaceutical Division, The Borden Company, New York, New York
Discussion to be opened by E. E. SEIDMON, M.D., Plainfield, New Jersey

9:30—A Review of the Immunologic Aspects of Thyroiditis
CHARLES A. OWEN, JR., M.D., Consultant in Experimental Biochemistry, Mayo Clinic, Rochester, Minnesota

10:10—A Clinical Study of a New Antihistamine, Dimethpyrindene
J. WARRICK THOMAS, M.D., Assistant Clinical Professor of Medicine, Medical College of Virginia, Director of the Thomas Clinic, Richmond, Virginia
FRANK R. KELLY, JR., M.D., Clinical Instructor in Medicine, Medical College of Virginia, Richmond, Virginia

10:30—RECESS TO VISIT EXHIBITS

11:00—Clinical Evaluation of Clysmathane
RICHARD H. JACKSON, M.D., Houston, Texas
HOMER E. PRINCE, M.D., Crockett, Texas

11:20—Gel Diffusion Precipitin Methods in the Study of Reagin
M. A. KAPLAN, M.D., R. K. JENNINGS, M.D., A. R. GOLDFARB, M.D., and M. GOLDIN, M.D., Chicago, Illinois

11:40—Studies with a New Bronchodilator Analog of Ephedrine, Isopro-Phenamine Hydrochloride, in Children
BENNETT KRAFT, MD., and JAMES G. ARMSTRONG, M.D., Indianapolis, Indiana
Discussion to be opened by MERRILL M. FENTON, M.D., Detroit, Michigan

12:00—LUNCH

Afternoon Session

Chairman: DELBERT J. PARSONS, M.D., Springfield, Ohio

Co-Chairman: MAYER A. GREEN, M.D., Pittsburgh, Pennsylvania

2:00—Higher Dosage Levels for Co-Seasonal Treatment of Pollinosis
BERNARD M. ZUSSMAN, M.A., M.D., Adult Allergy Clinic, University of Tennessee; Allergy Consultant to USPHS Hospital, Memphis, Tennessee
Discussion to be opened by LEON UNGER, M.D., Chicago, Illinois

2:20—Causes of Death and Pathologic Findings in 304 Cases of Bronchial Asthma
JAMES W. MESSER, M.D., Madison, Wisconsin
GUSTAVUS A. PETERS, M.D., Rochester, Minnesota
WARREN A. BENNETT, M.D., Ogden, Utah
Discussion to be opened by GILES A. KOELSCHE, M.D., Rochester, Minnesota

2:40—Isolation and Purification of the Allergens of Giant and Short Ragweed
A. R. GOLDFARB, M.D., and M. A. KAPLAN, M.D., Chicago, Illinois

3:00—RECESS TO VISIT EXHIBITS

3:30—The Glucosteroid-Sparing Action of Hydroxyzine in Bronchial Asthma
MILTON M. HARTMAN, M.D., Assistant Clinical Professor of Medicine, Stanford University School of Medicine, San Francisco, California

3:50—Anaphylactic Allergic Reactions to Influenza Vaccine
JOSEPH H. FRIES, M.D., Brooklyn, New York
MONROE COLEMAN, M.D., Stamford, Connecticut
Discussion to be opened by HARRY L. ROGERS, M.D., Philadelphia, Pennsylvania

4:10—The Reproducibility of Intradermal Skin Tests: A Controlled Study
PHILIP M. GOTTLIEB, M.D., F.A.C.P., Associate Allergist, Albert Einstein Medical Center, Philadelphia, Pennsylvania; Associate in Medicine, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania.
SONIA STUPNIKER, M.D., Adjunct in Allergy, Albert Einstein Medical Center, Philadelphia, Pennsylvania
S. I. ASKOVITZ, M.D., Medical Statistician, Albert Einstein Medical Center, Philadelphia, Pennsylvania

4:40—Impaired Hearing as a Manifestation of Allergy
ALEXANDER R. ALTOSE, M.D., Clinical Instructor in Medicine, Department of Medicine, University of Washington, Seattle, Washington
Discussion to be opened by M. COLEMAN HARRIS, M.D., San Francisco, California

PRELIMINARY PROGRAM

THURSDAY, MARCH 3, 1960

Morning Session

GENERAL SCIENTIFIC PROGRAM

Chairman: MORRIS A. KAPLAN, M.D., Chicago, Illinois

Co-Chairman: CLIFFORD H. KALB, M.D., Milwaukee, Wisconsin

9:00—Demethylchlortetracycline in Allergies Associated with Infection
WILLIAM C. GRATER, M.D., Dallas, Texas
CECIL M. KOHN, M.D., Kansas City, Missouri

9:20—Pollen Immunization with Emulsified Extracts
JOHN H. MITCHELL, M.D., WILLIAM F. MITCHELL, M.D., ROBERT BOLINSKE, M.D., and LYLE BURROUGHS, M.D., Columbus, Ohio

9:35—The Treatment of Allergic Patients with Emulsified Extracts of Pollens, House Dusts, Animal Danders and Influenza Virus Vaccine
ETHAN ALLAN BROWN, M.R.C.S., (England), L.R.C.P., (London), Boston, Massachusetts

9:50—Recent Therapeutic Experiments with Mineral Oil Emulsions of Inhalant Allergens
MARY HEWITT LOVELESS, M.D., Associate Professor of Clinical Medicine, Cornell University Medical College, New York, New York
Discussion of these three papers to be opened by FRANK F. FURSTENBERG, M.D., Baltimore, Maryland, and LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

10:30—RECESS TO VISIT EXHIBITS

PAPERS OF ASSOCIATE FELLOWS

11:00—A Prototype of an Asthmatic Unit in a General Pediatric Convalescent Home
MARTIN GREEN, M.D., Associate in Pediatrics, Jefferson Medical College, Pediatric Allergist, BETTY BACHARACH HOME, Chief of Pediatrics, Atlantic City Hospital, Atlantic City, New Jersey

11:15—Oral Decongestant Therapy in Respiratory Allergic Disease of Children
ARTHUR LIPSCHUTZ, M.D., Associate Professor of Pediatrics, Hahnemann Medical College, Philadelphia, Pennsylvania

11:30—Bronchial Asthma Complicated by Pectus Excavatum
LOUIS H. WINKLER, JR., M.D., Bethlehem, Pennsylvania

11:45—Food Allergy in Pediatric Practice
FRANCIS J. WAICKMAN, M.D., Cuyahoga Falls, Ohio

12:00—The Treatment of Hay Fever with Emulsified Extracts of Pollen
SOLOMON ARONOFF, M.D., Assistant Professor of Clinical Medicine, Seton Hall College of Medicine and Dentistry, Chief, Allergy Clinic, Medical Center, Jersey City, New Jersey

12:15—LUNCH

PRELIMINARY PROGRAM

Afternoon Session

Chairman: LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

Co-Chairman: GILES A. KOELSCHE, M.D., Rochester, Minnesota

2:00—Presidential Address
CECIL M. KOHN, M.D., President, The American College of Allergists, Inc., Kansas City, Missouri

2:20—A Cavalcade of Some Hormones and Steroids
Guest Speaker—EDWARD C. KENDALL, Ph.D., D.Sc. Visiting Professor of Physiological Chemistry, The James Forrestal Research Center, Princeton, New Jersey; Emeritus Professor of Biochemistry, Mayo Foundation, Rochester, Minnesota

3:00—Presentation Bela Schick and Clemens von Pirquet Awards

3:30—Annual Business Meeting of Members

7:00—BANQUET

FRIDAY, MARCH 4, 1960

Morning Session

TECHNOLOGY SESSION

Chairman: STEPHAN D. LOCKEY, M.D., Lancaster, Pennsylvania

Co-Chairman: LEON UNGER, M.D., Chicago, Illinois

9:00—Serial Titrations as a Guide to Pollen, Mold and Dust Desensitization
GEORGE S. FRAUENBERGER, M.D., St. Francis Hospital, Evanston, Illinois

9:20—Relief of Bronchial Asthma by Means of Mechanical Aids
CLIFFORD H. KALB, M.D., Attending Physician (Allergy) St. Joseph's Hospital, Milwaukee, Wisconsin

9:40—Skin Tests, Demonstrations of Techniques, Evaluations and Precautions
MAYER A. GREEN, M.D., Instructor in Dermatology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Clinical Assistant Professor, Section of Allergy, Department of Dermatology of the University of Pittsburgh School of Medicine

10:00—Technique of Preparing Alcoholic Solutions of Plants for Patch Testing
HENRY D. OGDEN, M.D., Assistant Professor, Department of Medicine, Louisiana State University, School of Medicine, New Orleans, Louisiana

10:10—RECESS

10:30—Panel—Specific Hyposensitization by Standard and Repository Means

Moderator—STEPHEN D. LOCKEY, M.D., Chief of Allergy, Lancaster General Hospital, Lancaster, Pennsylvania

M. COLEMAN HARRIS, M.D., Attending Physician and Chief of the Department of Allergy, San Francisco Polyclinic and Post-Graduate College; Attending Physician in Medicine (Allergy) Children's Hospital, San Francisco, California

MAYER A. GREEN, M.D., Instructor in Dermatology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania; Clinical Assistant Professor, Section of Allergy, Department of Dermatology of the University of Pittsburgh School of Medicine

HOMER E. PRINCE, M.D., Clinical Professor of Medicine, Baylor University College of Medicine, Houston, Texas

NATHAN SCHAFFER, M.D., Chief of Allergy at Orange Hospital, Central and East Orange General Hospital, East Orange, New Jersey

LEON UNGER, M.D., Associate Professor, Department of Medicine, Northwestern University, Chicago, Illinois

ETHAN ALLAN BROWN, M.R.C.S., (England), L.R.C.P., (London), Boston, Massachusetts

FRIDAY, MARCH 4, 1960

Morning Session

PEDIATRIC ALLERGY

Chairman: HOWARD G. RAPAPORT, M.D., New York, New York

Co-Chairman: JEROME GLASER, M.D., Rochester, New York

8:00—Breakfast—Sponsored by Syntex Chemical Company

9:00—Problems in the Management of Severe Allergic Dermatitis
HAROLD LECKS, M.D., Children's Hospital, University of Pennsylvania, Philadelphia, Pennsylvania

9:20—Nasal Allergy in Childhood (Experiences in Florida)
MEYER B. MARKS, M.D., Miami Beach, Florida

9:40—Nasal Allergies in Infants and Children with an Analysis of 400 Cases
JOHN P. MCGOVERN, M.D., Houston, Texas
THOMAS R. MCELHENNEY, M.D., Austin, Texas
KENNETH C. BURDON, PH.D., Houston, Texas

10:05—A Critical Evaluation of the Complications of Cortico-Steroid Therapy
SAMUEL C. BUKANTZ, M.D., Denver, Colorado

10:25—COFFEE BREAK—Courtesy of Syntex Chemical Company

10:45—Adrenal Function in Allergy. IV. Observations of Plasma Corticosterone and Cortisol in Asthmatic Children
SHELDON C. SIEGEL, M.D., Los Angeles, California
BAILEY J. LOVIN, JR., M.D., Los Angeles, California
VINCENT C. KELLY, M.D., PH.D., Los Angeles, California
ROBERT S. ELY, M.D., Los Angeles, California

11:05—A Comparison of Skin Reactions by Iontophoresis, Scratch and Intradermal Techniques
SUSAN DEES, M.D., and JOHN EVANS, M.D., Durham, North Carolina

11:30—The Allergic Diathesis and Its Relationship to Variations in Blood Gammaglobulin Levels
ARTHUR A. GOLDFARB, M.D., Bronx, New York
HUGH FUDENBERG, M.D., New York, New York
HENRY KUNKLE, M.D., New York, New York

12:15—LUNCHEON
Ontogency of Specific Immunity
DR. RICHARD T. SMITH, Professor and Chairman, Dept. of Pediatrics, University of Florida

FRIDAY, MARCH 4, 1960

Morning Session

ALLERGY OF THE NERVOUS SYSTEM

Chairman: THERON G. RANDOLPH, M.D.

Co-Chairman: STANILAUS H. JAROS, M.D.

9:00—Allergy and Epileptiform Seizures in Children
CLIFTON R. BROOKS, M.D., Newark, Delaware

9:20—DISCUSSION

9:30—Headaches and Allergy
WILLIAM MESSER, M.D., Brooklyn, New York

9:50—DISCUSSION

10:00—RECESS

10:10—Panel: Allergy and Demyelinating Diseases

The Clinical Aspects of Demyelinating Disorders
PERITZ SCHIENBERG, M.D., Professor of Neurology, University of Miami School of Medicine, Miami, Florida

Allergic Encephalomyelitis—An Experimental Model
MARIAN W. KIES, PH.D., Chief of the Section on Biochemistry, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Maryland

A History Pattern in Multiple Sclerosis Suggesting Susceptibility to the Chemical Environment.
THERON G. RANDOLPH, M.D., Chicago, Illinois

An All-inclusive Treatment of Multiple Sclerosis
S. WILLIAM SIMON, M.D., Dayton, Ohio

11:30—DISCUSSION

12:00—Business Meeting

PRELIMINARY PROGRAM

FRIDAY, MARCH 4, 1960

Afternoon Session

PSYCHOSOMATIC MEDICINE

Chairman: MILTON J. STEINHARDT, M.D., Detroit, Michigan
Co-Chairman: GRACE TALBOT, M.D., San Francisco, California

2:00—Emotional Aspects of Perennial Allergic Rhinitis and Bronchial Asthma
Guest Speaker: HERMAN SELINSKY, M.D., Analyst, Miami, Florida
Discussant: MURRAY PESHKIN, M.D., New York, New York

2:45—Panel Discussion: Perennial Respiratory Allergy, Basic Mechanism and Management
Moderator: MILTON J. STEINHARDT, M.D., Detroit, Michigan

Etiologic Factors
JOHN MITCHELL, M.D., Columbus, Ohio

Management of the Adult
FRANK F. FURSTENBERG, M.D., Baltimore, Maryland

Management of the Child
HOWARD RAPAPORT, M.D., New York, New York

Management, Psychotherapeutic of the Parents of the Child
HYMAN MILLER, M.D., Beverly Hills, California, and DOROTHY BARUCH, PH.D., Beverly Hills, California

3:45—QUESTIONS AND DISCUSSION WITH AUDIENCE PARTICIPATION

FRIDAY, MARCH 4, 1960

Afternoon Session

DERMATOLOGIC ALLERGY

Chairman: MAURICE C. BARNES, M.D., Waco, Texas
Co-Chairman: LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

2:00—Drug Reactions
MASON I. LOWANCE, M.D., Lowance Clinic, Atlanta, Georgia

2:30—Eczematous Eruptions of the Hands and Feet
ROBERT R. KIERLAND, M.D., Professor of Dermatology and Syphilology, University of Minnesota Graduate School of Medicine (Mayo Foundation), Rochester, Minnesota

3:00—Photosensitivity and Light Eruptions
C. BARRETT KENNEDY, M.D., Professor of Dermatology and Syphilology, Louisiana State University School of Medicine, New Orleans, Louisiana

3:30—Cortico-Steroids in the Treatment of Allergic Dermatoses
SIDNEY OLANSKY, M.D., Professor of Medicine (Dermatology), Emory University School of Medicine, Atlanta, Georgia

4:00—Chronic Urticaria as a Manifestation of the Stress Syndrome
WILLIAM L. POOLE, M.D., Instructor in Dermatology, Medical College of Alabama, Birmingham, Alabama

4:30—Contact Shoe Dermatitis: A Practical Approach to a Common Problem
JOHN H. HICKS, M.D., Clinical Assistant Professor of Dermatology, University of Miami School of Medicine, Miami, Florida

Technical Exhibits

Allergy-Free Products for the Home.....Brooklyn, N. Y.
Almay Division, Schieffelin & Co.....New York, N. Y.
Ar-Ex Products Co.....Chicago, Illinois
Ayerst Laboratories.....New York, N. Y.

Bird Oxygen Breathing Equipment, Inc.....San Francisco, Calif.
The Borden Company.....New York, N. Y.
George A. Breon & Co.....New York, N. Y.
Brewer & Company, Inc.....Worcester, Mass.
Burroughs Wellcome & Co. (U. S. A.).....Tuckahoe, N. Y.

G. W. Carnrick Co.....Newark, N. J.
Center Laboratories, Inc.....Port Washington, N. Y.
Ciba Pharmaceutical Products, Inc.....Summit, N. J.
The Coca-Cola Company.....Atlanta, Georgia

Desitin Chemical Company.....Providence, R. I.
The DeVilbiss Company.....Somerset, Pa.
Dome Chemicals, Inc.....New York, N. Y.

Eisele & Company.....Nashville, Tenn.
Endo Laboratories, Inc.....Richmond Hill, N. Y.

C. B. Fleet Co., Inc.....Lynchburg, Va.

Hugh Graham, Inc.....Dallas, Texas
Great Books of the Western World.....Baltimore, Md.

Hollister-Stier Laboratories.....Philadelphia, Pa.

Jackson-Mitchell Pharmaceuticals, Inc.....Culver City, Calif.

Knoll Pharmaceutical Company.....Orange, N. J.

Eli Lilly and Company.....Indianapolis, Ind.
Loma Linda Food Company.....Arlington, Calif.

McNeil Laboratories, Inc.....Philadelphia, Pa.
Merck Sharp & Dohme.....Philadelphia, Pa.

Organon, Inc.....Orange, N. J.

Parke, Davis & Company.....Detroit, Mich.
Pfizer Laboratories.....Brooklyn, N. Y.

Ralston Purina Company.....St. Louis, Mo.
A. H. Robins Company, Inc.....Richmond, Va.
J. B. Roerig and Company.....New York, N. Y.

Sandoz Pharmaceuticals.....Hanover, N. J.
Schering Corporation.....Bloomfield, N. J.
G. D. Searle & Co.....Chicago, Illinois
Sherman Laboratories.....Detroit, Mich.

Texas Pharmacal Company, Allercreme Division.....San Antonio, Texas

The Upjohn Company.....Kalamazoo, Mich.

Westwood Pharmaceuticals.....Buffalo, N. Y.
Winthrop Laboratories.....New York, N. Y.

Papers of Interest

Dekker, E., and Groen, J.: Reproducible psychogenic attacks of asthma. J. Psychosom. Res., 1:58-67 (Feb.) 1956.

In twelve patients with bronchial asthma (type not listed), the effect of psychologic stimuli on respiratory function, as measured by the vital capacity, was determined on the basis of the patient's emotional history. In six there were no reactions, in three minor reactions, and in three frank asthmatic attacks. Tense emotion was not sufficient to cause asthma unless associated with specific sensory stimuli. Two patients reacted to the inhalation of one or more allergens. The division of asthma into psychic and allergic types is regarded as unjustified.

Stocks, P.: Cancer and bronchitis mortality in relation to atmospheric deposit and smoke. Brit. M. J. 1:74 (Jan. 10) 1959.

Both factors statistically significant.

Burston, J., Husain, O., Hutt, M., and Tanner, E.: Two cases of auto-immune haemolysis and aplasia. Brit. M. J., 1:83 (Jan. 10) 1959.

Does an antibody produce destruction of red-cell precursors in the bone marrow and lead to increased erythrocyte mortality? Are Allergists hesitant to explore this relatively recently opened field, research in which will probably illuminate all aspects of allergy?

Nossal, G.: Antibody production by single cells. Brit. J. Exper. Path., 39:544 (Oct.) 1958.

Of 416 single rat lymph node cells, 56 produced antibodies against two types of Salmonella. In those animals immunized against both, not one of 326 single cells produced antibodies against either.

Bourne, M. and Dawson, H.: Acute pancreatitis complicating prednisolone therapy. Lancet, 2:1209 (Dec. 6) 1958.

A nephritic patient treated with prednisolone developed pancreatitis, which should be suspected if such patients develop abdominal symptoms.

Cohen, A.: Perphenazine in allergic conditions. Internat. Rec. Med., 172:33 (Jan.) 1959.

Perphenazine was given to 324 patients with allergies. In initial doses of 6 mg. reduced to 4 and 2 mg., it was found to be a useful ataractic in allergic patients.

Marti, H.: The anemia of chronic phenacetin abuse. Schweiz. med. Wchnschr. 88:1054 (Oct. 18) 1958.

Large amounts of phenacetin cause hemolytic anemia in 50 per cent of patients who use it for a long period of time.

Plaa, G., Fujimoto, J, and Hine, C.: Intoxication from primidone due to its biotransformation to phenobarbital. J.A.M.A. 168:1769 (Nov. 29) 1958.

Three cases of epileptics given the drug for anticonvulsant purposes and reacting with proven signs and symptoms of phenobarbital intoxication due to *in vivo* conversion.

Franklin, A.: The prognosis of bronchiectasis in childhood. Arch. Dis. Childhood, 33:19, 1958.

Of 171 bronchiectatic patients aged 5 to 8 years, 38 were graded as invalids, 70 delicate, and 63 well. Three to ten years later, 3 had died and 15 were classified as invalids, 23 as delicate, and 130 as well.

Halpern, B., Holtzer, A., Liacopoulos, P., and Meyer, J.: Allergy to pyrazolone derivatives (aminopyrine) with evidence of a reaginic type antibody. J. Allergy, 29:1, 1958.

Scratch tests revealed sensitivity to aminopyrine, iodoantipyrine, and antipyrine. The reagin-type antibody is thermolabile and destroyed by heating at 58° C.

Sidransky, H. and Friedman, L.: The effect of cortisone and antibiotic agents on experimental pulmonary aspergillosis. Am. J. Path., 35:169 (Jan.-Feb.) 1959.

In mice pretreated with cortisone and antibiotic agents, susceptibility to airborne saprophytic fungi is increased. Possibly true of human patients.

Poos, E.: Stress factors in rhinology. Ann. Otol., Rhin. & Laryng., 67:1073 (Dec.) 1958.

Rhinological practice looked upon from the point of view of Selye's general adaptation syndrome.

Ling, N.: The backbone of the antibody. Lancet, 2:1281 (Dec. 13) 1958.

Can antibodies be grouped, not according to adaptation to physiochemical surfaces, but rather by actual structure?

Perry, H., and Winkelmann, R.: Adverse reactions to sulfamethoxypyridazine (kynex). Its use in the treatment of dermatitis herpetiformis. J.A.M.A., 169:127 (Jan. 10) 1959.

Dermatitis herpetiformis can be controlled with sulfamethoxypyridazine, but reactions affecting skin and blood limit general use.

Greendyke, R., and Kaltreider, N.: Chronic histoplasmosis. Report of a patient successfully treated with amphotericin B. Am. J. Med., 26:135 (Jan.) 1959.

Chronic histoplasmosis which affected lung, other parts of the respiratory tract, and other organs and glands evidentally treated with success.

Kotin, P., and Falk, H. L.: Cancer, 12:147 (Jan.-Feb.) 1959. The role and action of environmental agents in the pathogenesis of lung cancer, I. Air pollutants.

Suggests series of causes, namely "susceptibility," acted upon by "environment" and by "agent."

Chaplin, H. Jr.: Studies on the survival of incompatible cells in patients with hypogammaglobulinemia. Blood, 14:24 (Jan.) 1959.

Suggests that search may unearth isoantibodies which will prove that hypogammaglobulinemic patients may not be true "universal recipients."

Brown, H. M.: Treatment of chronic asthma with prednisolone. Lancet, 2:1245 (Dec. 13) 1958.

Studies in 90 patients show that those in whom the sputum contains eosinophil cells respond more satisfactorily to prednisolone.

Freedman, D. X., and Fenichel, G.: Effect of midbrain lesion of experimental allergy. Arch. Neurol. & Psychiat., 79:164, 1958.

It is concluded from lesions placed in the midbrains of 17 sensitized guinea pigs that there is both augmentation and diminution of afferent and efferent responses to an allergenic bronchospasm. It is suggested that in allergic subjects the midbrain may similarly over-respond.

Ritchie, J. M.: The common cold: new approaches to prevention. Pfizer Spectrum, 7:2, 34 (Feb.) 1959.

A new approach, and a common-sense one.

Schirger, A., Martin, W. and Nichols, D.: Antibiotic therapy: clinical application of available agents. GP, J. Am. Acad. Gen. Pract., 19:102 (Feb.) 1959.

Although penicillin is the most used antibiotic agent, penicillin-resistant staphylococci can be affected by novobiocin, chloromycetin, kanamycin and ristocetin.

Horstman, H.: Clinical observations with dimetane. A new antihistaminic compound. Am. Practitioner, 10:96 (Jan.) 1959.

Satisfactory responses to the drug were seen, respectively, in 88, 90 and 83 per cent of patients suffering from pollinosis, perennial allergic coryza and chronic urticaria. Of 55 patients, two-thirds described dimetane as not only more effective, but causing fewer side effects.

Lincoln, C., Nordstrom, R. and Batts, E.: Treatment of itching. A preliminary report on results with a new oral antipruritic. California Med., 90:126 (Feb.) 1959.

In 70 per cent of 215 patients, trimeprazine relieved pruritus.

News Items

AMENDMENTS TO COLLEGE BY LAWS PROPOSED BY THE COMMITTEE ON BY LAWS

Article VI, Section 2 of the College By Laws, reads as follows:

The Committee on By Laws shall be composed of three members: the Chairman of the Board of Directors, who shall be its chairman, the chairman of the Finance Committee, and a third member who shall be the Director, other than the President, who is also in that year a member of the Board of Regents. This Committee shall hold at least one meeting in each year, immediately preceding the annual business meeting of the College, and may hold such additional meetings whenever and wherever members of this Committee have occasion to meet, including interim meetings of the Board of Directors, whenever such meetings are held.

The three members of this committee, Drs. Merle W. Moore, chairman, Lawrence J. Halpin and Mayer A. Green, had occasion to be at the administrative and business office of the College in Boulder, and also in nearby Denver, on November 6-7, 1959. Drs. Moore and Green attended the interim meeting of the Board of Directors which convened in Boulder on November 6, and Dr. Halpin was also there to attend a Fall meeting of the Finance Committee held at the same time at the office of the Treasurer, Dr. John D. Gillaspie. The three thereupon arranged to hold a meeting of the By Laws Committee on Saturday morning, November 7, 1959, in the Gold Room on the Mezzanine floor of the Brown-Palace Hotel.

I was present at these meetings in Boulder and Denver because, as Counsel for the College, I am required to attend all meetings of the Board of Directors and of the By Laws Committee. At the request of the Committee, I have prepared a written report of the November 7 meeting for submission to the Board of Regents.

While this report, with the recommendations made therein, will not be set forth herein in its entirety, it is, however, essential that certain of the resolutions adopted by the Committee (in which the Board of Regents is urged to modify, alter and amend the College By Laws to the extent and in the respects herein set forth and embodied in the report) be published in this issue of the ANNALS.

The reasons for publication thereof are three-fold:

1. It will bring these proposed By Law changes to the attention of all members, thereby enabling any and all who do not favor the amendments, full opportunity to seasonably voice their objections thereto, and those who do favor them, similar opportunity to express their approval.

2. Since the Board of Directors, by a resolution unanimously adopted at its interim meeting, has already given these changes its full approval and support and recommended their adoption, it is assumed that in the absence of well-grounded objections thereto the Board of Regents will modify, alter and amend the By Laws in the respects hereinafter set forth at its forthcoming annual meeting which will be held at the Americana Hotel on Tuesday, March 1, 1960.

3. To make it possible for these proposed amendments to be considered by the general membership if it so desires, and action to be taken thereon legally by the voting Fellows at the next annual business meeting of the College to be held on Thursday, March 3, 1960, at 3:00 p.m., the publication thereof in this issue of the ANNALS shall

(a) by reference be made a part of, and included in the call of the annual business meeting, notice of which appears elsewhere in this issue, all in conformity with the requirements of Article VIII of the College By Laws entitled "Amendments," and
(b) constitute notice thereof to each member, by publication, with the same legal force and effect as if each had been served personally with such notice in writing.

The proposed amendments follow:

1. The duties and functions of the Technological, Audio Visual, Publicity and Education Committees shall be spelled out by adding to Article VI in separately numbered paragraphs, beginning with number 8, the following additional sections:

Section 8. Technological Committee

It shall be the function of this committee to make available facts, data and opinions with respect to timely and adequate technological procedures used in the diagnosis, study and treatment of allergic disorders; included therein will be skin testing, laboratory studies and procedures, and the use of mechanical apparatus.

Section 9. Audio Visual Committee

This committee shall be set up to explore the availability of, and make effective recommendations for, the utilization and distribution of medical films and slides of particular or special interest to allergists. It may outline methods and organize procedures for securing the ethical showing of medical films and slides having to do with the observation, diagnosis and treatment of allergic disorders, and the establishment of a College library of such films and slides. It shall also recommend a list of films which it considers suitable for presentation at the annual instructional and scientific sessions of the College.

Section 10. Publicity Committee

This committee shall have general supervision of the preparation and distribution of all news releases, medical information and other data growing out of, or having to do with, any and all College activities, including meetings and conventions. It shall supervise and direct all publicity contacts, both lay and medical, with publishers, the press, radio, television, pharmaceutical houses, commercial establishments, and other similar organizations.

Section 11. Education Committee

This committee shall supplant the Public Education Committee and concern itself primarily with undergraduate, graduate, and postgraduate education in the field of allergy. It shall make recommendations with respect to the undergraduate teaching of allergy, the establishment of residencies in allergy, and the establishment of sectional postgraduate "instructional courses." It may make such recommendations and suggestions as it deems wise and proper with respect to the participation of allergists in general postgraduate courses.

2. Article VI, Section 1, entitled "Finance Committee" to be amended by deleting therefrom the first sentence of the third paragraph and inserting in lieu thereof the following:

"The Finance Committee shall hold at least one meeting annually, and, under the conditions herein set forth, may, in addition, hold one interim meeting in each calendar year. The annual meeting shall be held at a time to be fixed by the chairman during and in connection with the annual Congress of the College immediately preceding the annual meeting of the Directors and the annual meeting of the Regents which follows it. If there are matters of urgent importance which must be considered and acted upon before the end of any calendar year an interim meeting of the Finance Committee may then be held some time between the first day of November and the thirty-first day of December of that year, but only if, in the opinion of at least two (2) of the following three (3) officers—the Chairman of the Finance Committee, the Treasurer, and the Executive Vice President—these matters of business are considered to be of sufficient urgency or importance to require the holding of such a meeting. If any two (2) of these three (3) officers

determine such a meeting is required then Counsel shall immediately notify the Chairman of the Finance Committee in writing, instructing him to call the same. It shall be held at the business and administrative office of the College at a time to be fixed by the Chairman, but not earlier than 'the month of November nor later than the month of December of such year.' At such interim meeting (if none is held, then at its next annual meeting) the Finance Committee shall examine the College records, arrange for an annual audit of the College books as of the close of the current fiscal year, prepare the budget for the ensuing fiscal year, and generally transact such business having to do with the financial affairs and the business of the College as may come before it."

I think it of great significance, and worthy of special mention, that the members of the Finance Committee, Drs. Lawrence J. Halpin, Chairman, Ethan Allan Brown and Orval R. Withers, included in their recent report the very recommendations which have since led to the adoption of the resolution set forth in paragraph 2 above by the Committee on By Laws. These recommendations were made in the sincere belief that prudent management of College funds dictated that in future years interim meetings of the Finance Committee not be held unless matters of real urgency and importance arise to justify the expense thereof; that certain economies would result if the business customarily transacted at such interim meetings were deferred until the Committee members, without any additional expense, could convene a meeting during the annual Congress, preferably at an early date during that period, and preceding the annual meetings of the Board of Directors and Board of Regents.

3. That Article VI entitled "Committees" be further amended by striking therefrom the present Section 8 entitled "Allergy Clinics Committee" because such a committee, if it still exists, no longer functions, and its existence should, therefore, be legally terminated.

4. That portion of Article V, Section (j) entitled "The Nominations of Officers," which requires notice of the official ballot to be given to all voting Fellows of the College either by publication thereof in the official organ of the College, ANNALS OF ALLERGY, or by mail not later than three (3) months before the ensuing election, be amended and changed by striking out the words "not less than three (3) months," and inserting in lieu thereof "not less than sixty (60) days."

5. Such additions to, or deletions from, the list of standing committees which appears in the first paragraph of Article VI, and the addition of such further numbered sections to this article, beginning with Section 8, and such minor corrections elsewhere in these By Laws, to assure consistency and conformity throughout, in the event the modifications, alterations, and amendments herein recommended are put into effect by the Board of Regents or the general membership at their respective annual meetings during the Annual Congress of the College, February 28 to March 4, 1960.

I hope I have made it perfectly clear that each and all of these proposed By Law changes and amendments are published herein in the exact form in which they appear in the written report of the November 7, 1959, meeting of the Committee on By Laws, which recommends their adoption, and once published in this issue of the ANNALS, these alterations and amendments may legally be made by the Board of Regents at its next annual meeting, March 1, 1960, and also by the membership at the next annual business meeting of the members, Thursday afternoon, March 3, 1960, at the Americana Hotel, Bal Harbour, Florida.

I would like to add, it is my studied conviction that these several amendments proposed and recommended, after long and careful consideration by the Committee on By Laws, and which have the unanimous approval and support of the Board of Directors, if now enacted will prove beneficial to, and further the best interests of the College, and I therefore urge their adoption *in toto*.

ELOI BAUERS, *Counsel*

(See page 128 for meeting notices)

BOOK REVIEWS

CLINICAL DERMATOLOGY FOR STUDENTS AND PRACTITIONERS. Harry M. Robinson, Jr., Raymond C. Robinson, 254 pages, 117 figures. Baltimore: William & Wilkins Co., 1959. Price, $8.50.

The University of Maryland has been noted for its outstanding dermatologic training of medical students. This book, by the chief of the department is co-authored by his associate professor. It follows the pattern of morphologic dermatology teaching used at the medical school.

The first forty-nine pages comprise eleven chapters on the "General Considerations" of the skin. These included allergy, mycology, etiology, anatomy, physiology, diagnosis, and therapy. The remaining 200 pages are devoted to morphologic dermatology.

The twelfth chapter lists the regional involvement of the common dermatoses. The thirteenth chapter lists differential diagnosis charts of annular lesions, linear lesions, grouped vesicles, umbilicated lesions; excoriated lesions, ulcers, and alopecias. The fourteenth chapter notes the disorders in which other landmarks are characteristic, such as scaling, hyper-pigmentation, atrophy, eruptions which rarely involve the face, and systemic diseases in which cutaneous lesions are prominent. Single chapters are devoted to macular eruptions, papular eruptions, vesicular eruptions, pustular eruptions, lesions involving the scalp and other hairy areas, lesions involving the mucous membranes, sweat gland lesions, nail lesions, tropical diseases, and peripheral-vascular diseases.

With this format, a reader who knows the difference between a papule and a macule should be able to study a patient with a skin eruption, and differentiate its type within a group of several possibilities. Reading a discussion in the chapters should lead to correct diagnosis in a high percentage of cases.

For non-dermatologists who must treat skin diseases, and are not sure what they are treating or why, the book should be of assistance. As obviously necessary when compressing wide subjects into narrow books, this work discusses each disease with a minimum of verbosity. There is no bibliography.

The illustrations are technically excellent. One criticism is common to many texts—that is that an illustration, for example, of squamous cell carcinoma, is chosen as taken from a lesion the size of a large orange. This late type of lesion—the type which brings whistles of amazement even from those used to the vicissitudes of patients treated on large charity services—is often selected for text book illustrations. It is not instructive for non-dermatologists, who will probably not see such a case once in their medical careers. Other than this, the pictures have been aptly selected to illustrate and make clear the diagnostic entity being discussed.

For an allergist who may be called upon involuntarily and unwillingly to practice some dermatology, this book is highly recommended as a guide and aid to the diagnosis of an unknown eruption, providing that some larger and more extensive textbook is also available, once the diagnostic entity has been chosen. Of special interest to the allergist will be the discussion of treatment of atopic eczema. The authors are to be congratulated on the completeness of their discussion. They include and reconcile multiple factors, notably steering between too much and too little emphasis on the psychogenic, and all in a space represented by two pages.

M.C.Z.